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Original Article

Hematological parameters and remission induction of childhood acute lymphoblastic leukemia

Roro R. W. Perdani, Bambang Sudarmanto

Abstract

Background High-risk acute lymphoblastic leukemia (ALL) is one of the most common childhood malignancies in Indonesia. Many factors can inhibit the induction of remission. Hematological parameters are usually not normal. Identification of corresponding factors is important to increase the likelihood of successful inductions.

Objective To assess for associations between hematological parameters and induction of remission in children with acute lymphoblastic leukemia.

Methods Data were collected from medical records of ALL patients hospitalized in the Pediatric Ward at Dr. Kariadi Hospital from May 2014 – May 2016. Dependent variables were hemoglobin, leukocytes, platelets, and absolute neutrophil count (ANC) levels; the independent variable was induction of remission.

Results Out of 55 patients, 33 (60%) had anemia, 6 (10.9%) had leukocytosis, and 1 (1.8%) had hyperleukocytosis, whereas 9 (34.5%) had leukopenia and 29 (52,7%) had normal leukocyte levels. Thirty-one subjects (56.4%) had thrombocytopenia, 15 (27.3%) had thrombocytosis, and only 9 (16.4%) patients had normal platelet counts. There were 29 (52.7%) with ANC > 500, whereas 26 (47.3%) had ANC level ≤ 500. Most patients (80%) experienced remission induction, while 20% did not. There were significant associations between ANC level and induction of remission (P=0.010) as well as between platelet level and induction of remission (P= 0.033). Regression logistic test revealed that ANC level ≤ 500 was associated with a 7-fold lower remission event compared to ANC level > 500 (RR 7.147; 95%CI 1.38 to 37.14).

Conclusion Lower ANC level (≤ 500) is significantly associated with lower remission compared to higher ANC level (> 500). **[Paediatr Indones. 2018;58:71-4; doi: http://dx.doi.org/10.14238/pi58.1.2018.71-4]**.

Keywords: *high-risk ALL; remission; induction; hematological parameters*

Leukemia is the most common malignancy in childhood.[1] From an epidemiological standpoint, acute leukemia occurs in 30%-40% of all childhood malignancies.[2-4] Standard and high-risk groups are widely known to have different outcomes, therapy, and even prognoses. The high-risk group has been linked to poor prognosis. High-risk ALL chemotherapy consists of the induction phase, consolidation, re-induction, and maintenance therapy, with each phase having its own goals. The main induction phase achievement in ALL chemotherapy is remission.[5-7] A remission failure could be caused by abnormal hematologic parameters, such as initial hemoglobin level, initial leukocytes and platelets, as well as low ANC level.[8] Identifying the corresponding factors is very important in order to increase the likelihood of remission.

Methods

This retrospective cohort study was conducted from May 2014 through May 2016. The inclusion criteria

From the Department of Child Health, Diponegoro University /Dr. Kariadi Hospital, Semarang Indonesia

Reprint requests to: Roro Rukmi WP, Department of Child Health, Diponegoro University/Dr. Kariadi Hospital, Jl. Dr. Sutomo 16, Semarang. Tel. +62-24-8413476; E-mail: rororwp@gmail.com.

were children between 0-18 years of age who were diagnosed with ALL at Dr. Kariadi Hospital, Semarang, had never undergone any Indonesian 2006 ALL chemotherapy protocols, and agreed to participate in the study. Hematologic parameters consisted of initial of hemoglobin, leucocyte, and platelet levels, and ANC level. Initial hemoglobin level was categorized anemic and non-anemic according to WHO criteria on age. Whereas initial leucocyte level was divided into normal (10,000 - < 50,000/mm^3), leukopenia (< 10,000/mm^3), leukocytosis (50,000-100,000/mm^3) and hyperleucocytosis (> 100,000/mm^3). The other parameter was initial platelet count which categorized into normal (150,000-400,000/mm^3), thrombocytopenia (< 150,000/mm^3) and thrombocytosis (> 400,000/mm^3). The outcomes of induction was remission and no remission. Remission was defined with the blast cell in bone marrow puncture 20%, while no remission was if the blast cell ≤ 20%. The diagnosis of high risk ALL was made using the *National Cancer Institute* (NCI) criteria: peripheral leukocyte count > 50,000/mm^3, children aged <1-year-old or ≥ 10-year-old, evidence of mediastinal mass, or blast cell absolute count in peripheral blood ≥ 1,000/mm^3. Patients lost to follow up or who died before undergoing induction therapy were excluded from this study.

The standard risk group was aged between 1 and 10 years and the high risk group was aged younger than 1 year or older than 10 years.

Data were collected from subjects' medical records. The dependent variables were hematologic parameters, consisting of initial hemoglobin level, initial leukocyte and platelet levels, and ANC; the independent variable was remission induction. Chi-square test or Fisher's exact test were used for bivariate analysis and relative risk; logistic regression test was used for multivariate analysis. A P value of < 0.05 is considered significant. This study was approved by the Research Ethics Committee of the Diponegoro University Medical School.

Results

During the 2 year study period, 55 children met the inclusion criteria. Baseline characteristics are shown in **Table 1**. Most subjects were in the standard risk group

Table 1. Baseline characteristics of subjects

Characteristics	n (%)	Mean (SD)	Median (range)
Age		6.96 (3.62)	6.58 (0-17.75)
Standard risk (1 to <10 years)	45 (81.8)		
High risk (<1 year or ≥10 years)	10 (18.2)		
Sex		8.91 (2.51)	9.4 (2.2-13.3)
Male	34 (61.8)		
Female	21 (38.2)		
Initial haemoglobin levels			
Anemic	33 (60)		
Non-anemic	22 (40)		
Initial leukocyte levels		39,944.24 (60,876.69)	9,000 (900-312,700)
Normal	29 (52.7)		
Leukopenia	19 (34.5)		
Leukocytosis	6 (10.9)		
Hyperleukocytosis	1 (1.8)		
Initial platelet counts		84,594.36 (101,068.48)	39,000 (190 – 352,000)
Normal	9 (16.4)		
Thrombocytopenia	31 (56.4)		
Thrombocytosis	15 (27.3)		
ANC count			
≤ 500	26 (47.3)		
> 500	29 (52.7)		
Induction outcomes			
Remission	44 (80)		
No remission	11 (20)		

(81.8%) and most were male (61.8%). Our subjects' median age was 6.58 years when diagnosed.

In the bivariate analysis, two factors were significantly associated with worse remission rates in the induction phase: platelet levels (thrombocytopenia) and ANC level <500 (**Table 2**). Further analysis by logistic regression test revealed that ANC level ≤500 was associated with a 7-fold lower remission event compared to ANC level >500 (RR 7.147; 95%CI 1.38 to 37.14) (**Table 3**).

Table 2. Bivariate analysis factors associated with induction of remission

Variables	Outcomes, n(%)		P value
	Remission (n=44)	No remission (n=11)	
Anemia			1.000
Yes	26 (59.1)	7	
No	18 (40.9)	4	
Leukocyte levels			0.122
Normal	26 (59.1)	3	
Leukopenia	14 (31.8)	5	
Leukocytosis	3 (6.8)	3	
Hyperleukocytosis	1 (2.3)	0	
Platelet levels			0.033
Normal	9 (20.5)	0	
Thrombocytopenia	21 (47.7)	10	
Thrombocytosis	14 (31.8)	1	
ANC count			0.010
> 500	27 (61.4)	2	
≤ 500	17 (38.6)	9	

Table 3. Multivariate analysis of factors associated with induction of remission

Variable	RR	95%CI	P value
ANC level	7.147	1.38 to 37.14	0.019

Discussion

In our study of 55 subjects, remission in the induction phase was achieved in 44 subjects (80%). Reports from developed countries also show remission rates in the induction phase to be approximately 80%.[6,7] A Busan, Korea study found that 43 (95.6%) patients achieved complete remission.[9] Our subjects' median age was 6.58 years when diagnosed, with an age range of 0-17.8 years. A previous study noted the mean age of subjects was 5.4 years at the time of diagnosis, with a range of 2 – 12 years.[10] The standard risk group comprised of 45 (81.8%) subjects, whereas the high risk group had 10 (18.2%) subjects, which consisted of 1 subject younger than 1 year and 9 subjects older than 10 years. Another study in Cipto Mangunkusumo Hospital, Jakarta, demonstrated different result of age groupings to those of our study, where most patients were between 2 and 10 years of age (59%).[11] In our study, 61.8% of subjects were male and 38.2% were female. Similarly, the distribution of male and female subjects in a Makassar study was 60% and 40%, respectively.[12]

Subjects' mean hemoglobin level was 8.91 g/dL (SD 2.51), and the median was 9.4 (range 2.2-13.3) g/dL. In a Korean study, the the median hemoglobin level was a similar 8.5 (range 3.2-14.7) g/dL.[9]

In our study, the majority of subjects (52.7%) had normal leukocyte levels. The remaining subjects had 34.5% leukopenia, 10.9% leukocytosis and 1.8% hyperleukocytosis. In contrast, a Surabaya study reported that 23.2% of subjects had leukocytosis, with leukocyte level of > 50,000/mm^3. Leukopenia was observed in 30% of their subjects.[5]

The majority of our subjects (56.4%) had thrombocytopenia, with mean platelet count of 84,594.36/mm^3. Again, our results differed from the Surabaya study. In their high risk ALL patients, the highest platelet levels were 50,000-100,000/mm^3, comprising 42.8% of the total subjects.[5]

Bivariate analysis showed that the ANC level ≤ 500 (P=0.010) and thrombocytopenia (P=0.033) were significantly associated with remission in the induction phase. In contrast, a study from Korea noted that initial leukocyte level was associated with event free survival, and high levels of leukocytes (10 x 10^9/L) could worsen the event free survival (EFS) (P<0.001).[9]

In conclusion, the study shows that ANC level of ≤ 500 is significantly associated with worse remission rate. The ANC level has been used to diagnose neutropenia. Patients with neutropenia are susceptible to infection and febrile neutropenia may occur.[13,14] In our subjects, it is possible that the association between ANC level ≤ 500 and worse remission rates was caused by severe infection that inhibited the remission by the end of induction phase. However, we did not analyze for an association between febrile neutropenia and remission in the induction phase.

Conflict of Interest

None declared.

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