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Original Article

Influence of initial treatment delay on overall survival and event-free survival in childhood acute lymphoblastic leukemia

Irenne Purnama, Pudjo Hagung Widjajanto, Wahyu Damayanti

Abstract

Background Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy. Initial treatment delay is a modifiable prognostic factor that significantly affects overall survival (OS) and event-free survival (EFS) of childhood ALL in high-income countries. Nevertheless, the effect of delayed initial treatment in low-middle income countries had not been determined.

Objective To analyze relationships between initial treatment delay with overall survival and event-free survival in children with ALL.

Methods A retrospective study was conducted in children aged < 18 years newly diagnosed with ALL L1 and L2 from January 2013 until December 2018 at Dr. Sardjito Hospital, Yogyakarta. Initial treatment delay was defined as a time interval of more than 3 days between diagnosis and treatment. The outcomes of the study were OS and EFS. Negative events were defined as remission failure, relapse, dropping out, and death. Overall survival (OS) and event free survival (EFS) were analyzed by Kaplan-Meier and log-rank tests.

Results Of 341 subjects, 188 (55.5%) underwent delayed initial treatment. There were no significant relationships between initial treatment delay and OS (HR 0.845; 95%CI 0.548 to 1.302; P=0.445) or EFS (HR 0.937; 95%CI 0.689 to 1.275; P=0.971). Multivariate analysis revealed that age was an independent prognostic factor for both OS (P<0.001) and EFS (P<0.001).

Conclusion Initial treatment delay is not associated with OS or EFS. Age is an independent predictor for both OS and EFS. **[Paediatr Indones. 2021;61:217-22 ; DOI: 10.14238/pi61.4.2021.217-22**].

Keywords: *initial treatment delay; childhood; ALL overall survival; event free survival*

Acute lymphoblastic leukemia (ALL) is the most common malignancy (26%) in children under the age of 15 years. *Surveillance, Epidemiology, and End Result* (SEER) data in the United States revealed that the incidence of ALL increased from 25 cases per 1 million children in 1975 to 34 cases per 1 million children in 2010.[1] The incidence of ALL in Jakarta was 27 cases per 1 million children in 1994, while that in Dr. Sardjito Hospital, Yogyakarta, was 19.2 cases per 1 million children in 1998 and 54.6 cases per 1 million children in 2009.[2] Although the incidence of ALL increased, the overall survival of ALL in developed countries also increased from 57% in 1975 to 90% between 2003 and 2009. This remarkable improvement was due to the discovery of important biologic subsets of ALL that further refine risk stratification and facilitate the combination of targeted molecular therapies with chemotherapy.[3]

From the Department of Pediatrics, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada University/Dr. Sardjito Hospital, Yogyakarta, Central Java, Indonesia.

Corresponding author: Irenne Purnama. Department of Child Health, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/ Dr. Sardjito Hospital. Jl. Kesehatan No.1, Senolowo, Sinduadi, Kec. Mlati, Kabupaten Sleman, Daerah Istimewa Yogyakarta 55281, Central Java, Indonesia. Phone: +62-274-583745. Email: irennepurnama@gmail.com.

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Unlike survival rates in developed countries, ALL survival rates in developing countries are lower. In 2005-2009, overall ALL survival varied in Asian countries from 18.7% in Mongolia to 84.4% in Japan. India's overall ALL survival in 2005-2009 was 83% and while that of Malaysia was 70.1%.[4] To our knowledge, ALL survival rates in Indonesia have never been reported. The survival rate in Jakarta in 2005-2009 was 44.3%.[4] The most recent data from Yogyakarta was in 2010-2015, with an ALL survival rate in Dr. Sardjito Hospital of 56.1 (SD 3.9) %.[5] The difference in survival rates between developing and developed countries is generally due to the former's limited diagnostic facilities, limited access to therapy, and low socioeconomic status.[6]

Because of the high morbidity and mortality caused by ALL, it is important to identify modifiable factors that influence the survival of ALL. One such factor is initial treatment delay. Delayed chemotherapy (≥3 days) from the time of established diagnosis until the first chemotherapy treatment was reported to worsen the survival of ALL patients (HR 2.49; 95%CI 1.40-4.43; P=0.002), whereas delayed diagnosis (time from patient admission to the time of established ALL diagnosis of ≥3 days) was reported to not affect the survival of ALL patients (HR 1.17; 95%CI 0.61-2.27; P=0.630).7 In our study, we analyzed for relationships between initial treatment delay with overall survival and event-free survival in children with ALL since initial treatment delay may be a risk factor that can be modified to increase the survival of childhood ALL.

Methods

A retrospective study was conducted in children aged 28 days to < 18 years, diagnosed with L1 or L2 ALL between January 1, 2013 and December 31, 2018, using the Hematology-Oncology Registry and medical records of Dr. Sardjito Hospital, Yogyakarta. Survival analysis was done with Kaplan-Meier and Cox regression. Total sampling was used as the sampling method. Subjects underwent the entire ALL Protocol from the beginning at Dr. Sardjito Hospital. Exclusion criteria were patients with incomplete medical record data and those who had received chemotherapy prior to ALL diagnosis.

The independent variable in this study was delayed initial chemotherapy (>3 days from ALL diagnosis through bone marrow aspiration to the initial administration of chemotherapy). Other variables examined were age at diagnosis, leukocyte count at diagnosis, immunophenotype, and steroid response at day 7. The dependent variables were OS and EFS. Overall survival was defined as the time from diagnosis to death or December 31, 2018 (cut-off date), while EFS was defined as the time from diagnosis to the first appearance of negative outcomes/events or December 31, 2018 (cut-off date). Negative events included death, remission failure, relapse, and dropping out. The Kaplan-Meier method was used to examine the relationship between time to treatment and OS and EFS. Differences between survival times were analyzed by log-rank test, with P values <0.05 indicating statistical significance. Variables with P values <0.25 in univariate analysis and the independent variable (delayed therapy) were included in multivariate analysis.

This study was approved by the Health Research Ethics Commission at the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/ Dr. Sardjito Hospital, Yogyakarta.

Results

Of 409 patients diagnosed with ALL in Dr. Sardjito Hospital, Yogyakarta, from January 2013 to December 2018, 68 patients were excluded because they had received therapy (steroids) before the diagnosis was made. Of the 341 study subjects, 188 patients (55.1%) experienced delayed therapy and 153 patients (44.9%) did not experience delayed therapy. The basic characteristics of the study subjects were obtained from medical records. The distribution of subjects according to sex, age, disease severity and protocol types is presented in **Table 1**.

Mean overall survival (OS) and event free survival (EFS) were 54.0 (SD 7.4) % and 8.2 (6.4) %, respectively. Kaplan Meier revealed no significant differences between the delayed and appropriate treatment groups in terms of OS (55.3% vs. 50.7%, respectively, P=0.455) or EFS (12.7% vs. 0%, respectively, P=0.679) (**Figures 1** and **2**).

Univariate analysis revealed that age at diagnosis was significantly associated with inferior OS and

Table 1. Baseline characteristics of subjects

Characteristics	Delayed therapy (n=188)	Appropriate therapy (n=153)	Total (N=341)	P value
Sex, n (%)				
Female	89 (47.3)	64 (41.8)	153 (44.9)	0.309
Male	99 (52.7)	89 (58.2)	188 (55.1)	
Age at diagnosis, n (%)				
<1 year or >10 years	37 (19.6)	33 (21.6)	70 (20.5)	0.668
1-10 years	151 (80.3)	120 (78.4)	271(79.5)	
WBC count at diagnosis, n (%)				
<50,000cells/µL	151 (80.3)	103 (67.3)	254(74.5)	0.006
≥50,000 cells/ µL	37 (19.7)	50 (32.7)	87(25.5)	
Immunophenotype, n (%)				
B cell	16 (8.5)	15 (9.8)	31(9.1)	0.784
T cell	37 (19.7)	28 (18.3)	65 (19.1)	
Mixed	15 (8.0)	15 (9.8)	30 (8.8)	
No data	120 (63.8)	95 (62.1)	215 (63)	
Response to initial therapy[a], n (%)				
Poor[b]	3 (1.6)	4 (2.6)	7 (2)	1.000
Good[c]	67 (35.6)	76 (49.7)	143 (42)	
No data	118 (62.8)	73 (47.7)	191(66)	
Risk stratification n(%)				
Standard risk	113 (60.1)	71 (46.4)	184 (54)	0.012
High risk[d]	75 (39.9)	82 (53.6)	157(46)	
ALL protocol, n (%)				
2013	103 (54.8)	69 (45.1)	172 (50.4)	0.186
2016	82 (43.6)	83 (54.2)	165 (48.4)	
No data	3 (1.6)	1 (0.7)	4 (1.2)	
Survivals				
Overall survival	55.3%	50.7%		
Mean (SD)	54.0 (7.4)			
P value	0.455			
Event free survival	12.7%	0%		
Mean (SD)	8.2 (6.4)			
P value	0.679			

[a]Assessed at the 8th day after receiving steroids and first dosage of intrathecal methotrexate (MTX);
[b]Poor response defined as absolute lymphoblast count ≥1,000 cells/mm^3 in peripheral circulation;
[c]Good response defined as absolute lymphoblast count <1,000 cells/mm^3 in peripheral circulation
[d]High risk : age < 1 year or > 10 years; white blood cells (WBC) count at diagnosis ≥50,000 cells/ µL ; mediastinal mass, meningeal leukemia, immunophenotype T cell ; poor response to initial therapy

EFS, with age <1 year or > 10 years vs. 1-10 years having OS 30.6% *vs.* 59.8%, respectively, (P<0.001), and having EFS 7.9 % *vs.* 9.7 %, respectively, (P<0.001). Furthermore, white blood cells (WBC) count at diagnosis (≥ 50,000 *vs.* <50,000 cells/µL) had significant univariate associations with OS and EFS [OS 57.3% *vs.* 45.2%, P=0.040; EFS 10.3% *vs.* 0%, P=0.016]. Univariate analysis showed that delayed therapy had no significant effect on either OS or EFS (P=0.445 and P=0.697, respectively). Multivariate analysis revealed that age <1 year and > 10 years at diagnosis remained independently associated with OS (HR 2.542; 95%CI 0.802 to 2102; P<0.001) and EFS (HR 1.961; 95%CI 0.921 to 1.866; P<0.001). However, multivariate analysis revealed that leukocyte count at diagnosis was not significantly associated with OS or EFS (**Tables 2** and **3**).

Discussion

In our study, the ratio of patients who experienced delayed initial chemotherapy compared with those who underwent appropriately-timed therapy was 1.2:1, with an overall median interval of 3 days from diagnosis to initial chemotherapy treatment. In

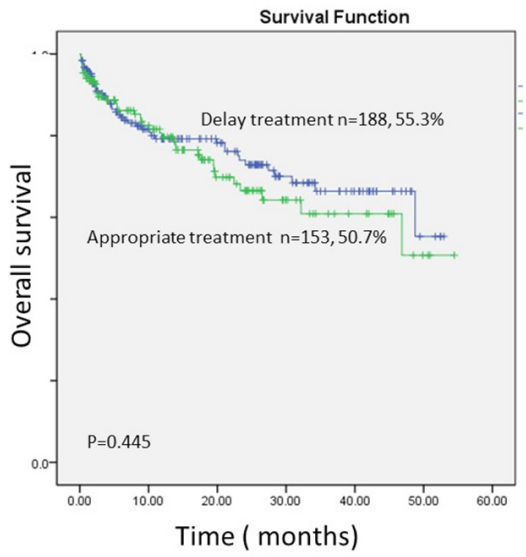

Figure 1. OS for delayed therapy

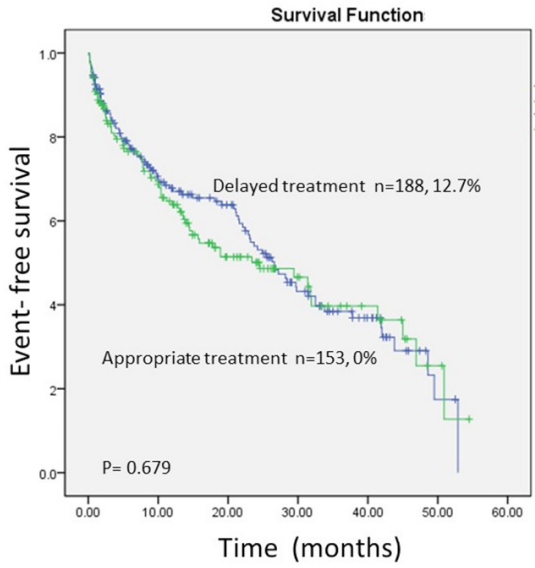

Figure 2. EFS for delayed therapy

Table 2. Univariate and multivariate analyses (Cox regression) for OS

Variables	N	Univariate			Multivariate		
		HR	95%CI	P value	HR	95%CI	P value
Time to treatment							
Delayed	188	0.845	0.548 to 1.302	0.445	0.915	0.592 to 1.414	0.689
Appropriate	153						
Sex							
Female	153						
Male	188	1.174	0.760 to 1.814	0.469			
Age at diagnosis							
<1 yr or >10 yrs	70	2.774	1.749 to 4.399	<0.001	2.542	0.802 to 2.102	<0.001
1-10 years	271						
WBC count at diagnosis							
≥50,000 cells/µL	87	1.624	1.023 to 2.579	0.040	1.298	0.802 to 2.102	0.288
<50,000 cells/µL	254						
Immunophenotype							
B cell	31						
T cell	65	1.635	0.686 to 3.898	0.267			
Mixed	30	0.559	0.177 to 1.770	0.323			
Response to initial therapya							
Poor	7	0.578	0.163 to 2.051	0.396			
Good	143						
ALL protocol							
2013	166	1.326	0.815 to 2.157	0.256			
2016	175						

contrast, in a Canadian study, only 72/980 subjects (7.4%) experienced delayed therapy (ratio 0.08:1), with a median interval of 1 day from diagnosis to initial chemotherapy.[7] These differences may have been due to income differences, as low-middle income countries often have limited diagnostic facilities, limited access to therapy, and lower economic status.[8] We found that delayed therapy was not associated with OS (55.3% delayed *vs.* 50.7% appropriate; P=0.445) or EFS (12.7% delayed *vs.* 0% appropriate; P=0.679). Our findings differed from previous study which showed that delayed therapy was associated with

Table 3. Univariate and multivariate analyses (Cox regression) for EFS

Variables	N	Univariate			Multivariate		
		HR	95%CI	P value	HR	95%CI	P value
Time to treatment							
Delayed	188	0.937	0.689 to 1.275	0.697	1.006	0.737 to 1.373	0.971
Appropriate	153						
Sex							
Female	153						
Male	188	1.127	0.827 to 1.536	0.447			
Age at diagnosis							
<1 yr or >10 yrs	70	2.120	1.490 to 3.018	<0.001	1.961	0.921 to 1.866	<0.001
1-10 years	271						
WBC count at diagnosis							
≥50,000 cells/μL	87	1.515	1.079 to 2.128	0.016	1.311	0.921 to 1.866	0.133
<50,000 cells/μL	254						
Immunophenotype							
B cell	31						
T cell	65	1.169	0.644 to 2.125	0.608			
Mixed	30	0.527	0.251 to 1.107	0.091			
Response to initial therapya							
Poor	7	0.197	0.027 to 1.416	0.106			
Good	143						
ALL protocol							
2013	166	1.130	0.790 to 1.610	0.497			
2016	175						

both worse OS (74.5% delayed *vs*. 92.3% appropriate; P<0.001) and worse EFS (71.8% delayed *vs*. 83.7% appropriate; P=0.025).[7] These differences may have been due to their larger sample size of 1,000 subjects compared to our 341 subjects. In addition, the number of patients who experienced delayed therapy in their study was very small compared to our study (7.3% *vs*. 55.1%, respectively). In their study, patients who experienced delays may have had quite severe disease characteristics requiring delayed chemotherapy, and not because of hospital service systems or healthcare-associated shortcomings. This Canadian study gave no explanation as to whether the two independent variable groups (delayed vs. appropriate therapy) had the same basic characteristics. Nor did they include subjects aged <1 year.[7] A previous study showed results similar to ours with no association between delayed initial therapy with relapse (P=0.80) or death (P=0.15). The delay of initial therapy was also not associated with the length of stay (P=0.08) or the incidence of bacteremia (P=0.07).[9] In our study, more patients with delayed initial therapy had better OS and EFS compared to those who underwent appropriately-timed therapy, but the difference was not significant. These findings may have been due to the larger number of patients with less severe disease characteristics (standard risk/SR) in the delayed treatment group, whereas the appropriately-timed therapy group had more patients with more severe disease characteristics (high risk/HR) (**Table 1**). It is well known that disease stratification at the diagnosis play a major role in influencing OS and EFS. Hence, risk group plays a role in influencing OS and EFS. Despite the lack of statistical significance, initial therapy should be administered as soon as possible after diagnosis.

Administration of prednisone and intrathecal MTX (ITMTX) marked the initiation of the protocol. Both agents reduce lymphoblast cells in both peripheral blood and bone marrow. Prednisone interferes with the cell cycle by suppressing the activity of transcription factors such as activating protein-1 (AP-1) or nuclear factor-κB (NF-κB), thereby inhibiting DNA transcription. Intrathecal MTX has a local effect to prevent CNS infiltration by inhibiting dihydrofolate reductase (DHFR) activity of converting folate to reduced folate (tetrahydrofolate). Folate deficiency inhibits de novo purine synthesis pathways, thus inhibiting DNA synthesis and the S phase (synthesis) in

the cell division cycle.[10] These two chemotherapeutic agents reduce the rate of proliferation at the onset of the induction phase protocol, further reducing complications caused by ALL at the initial diagnosis (bleeding, infection, anemia, and leukostasis) due to lack of erythropoiesis and thrombopoiesis in bone marrow caused by uncontrolled proliferation of lymphopoietic components. The decreased number of absolute lymphoblasts on peripheral blood smear at the 8th day after administration of steroids is indicative of the magnitude of the effect of steroid and ITMTX in killing circulating lymphoblasts. As such, timing can be a prognostic factor for OS and EFS in patients. Therefore, the accuracy of timely chemotherapy is important in clinical settings.

A limitation of this study was that not all prognostic factors known to affect OS and EFS were included as potential confounding factors. Other factors such as hemogloblin level, degree of thrombocytopenia, and nutritional status were not evaluated. Another limitation of this study was that using the time interval between diagnosis and initial chemotherapy may have decreased the accuracy of our study. Since our patients were in a referral hospital, a longer time interval (since symptoms were first experienced or since the patient first sought help from a healthcare provider) should be counted to make the result of the study statistically significant. Further study is needed to determine the optimal cut-off to define delayed initial therapy that can significantly affect survival in pediatric ALL patients. In conclusion, initial treatment delay has no associations with OS or EFS in children with ALL. Age at diagnosis is an independent prognostic factor of OS and EFS in children with ALL, with ages <1 year or >10 years being associated with worse OS and EFS.

Conflict of Interest

None declared.

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