Retrospective Study on Very Early Relapse of Childhood Acute Lymphoblastic Leukemia at a Reference Centre in Indonesia

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ABSTRACT

Introduction: The cure rate of Acute Lymphoblastic Leukemia (ALL) in low and middle-income countries is still low. Many factors contribute to relapses event, thus leading to failure of the treatment outcome. However, there are limited studies regarding the relapse of childhood cancer in Indonesia. This study determined demography, clinical, and characteristic laboratory differentiation between relapse and non-relapse in the bone marrow childhood ALL group.

Methods: This was a retrospective descriptive study in children newly diagnosed with ALL ages 0-18 who completed the induction phase using the 2013 treatment protocol during the 2018 period in Pediatrics Hematology-Oncology Unit at a reference center hospital in Indonesia. Of 78 data collected from the Indonesian Pediatric Cancer Registry (IP-CAR) and Hospital Information System after excluding abandoned treatment or death during treatment, only 35 patients completed the overall therapy. We evaluated bone marrow relapse and classified it into 'very early' relapse that occurs at least 18 months from diagnosis, 'early' relapse between 18 and 36 months, and more than 36 months is called 'late' relapse. Chi-square test was used to elaborate association between relapse and sex, leukocyte count, morphological classification, risk stratification, nutritional status. Kruskal Wallis tests were used to elaborate on the association between relapse, age, and induction duration. P value<0.05 was considered statistically significant.

Results: Among 35 patients in this study, seven patients experienced bone marrow relapse. Relapses were dominant in four male patients, four patients aged from 1-10 years old, six patients with leukocytes count below 50.000/mm^3, six normal nutritional status patients, and six patients classified as L2 patients. All relapse events occurred in a very early stage. Four patients are classified as standard risk, and three patients are high risk. There were no significant differences among characteristics of the relapse and non-relapse groups.

Conclusions: The observed relapse onset is less than 18 months from diagnosis (very early relapse) during maintenance treatment. However, we found no significant demography, clinical, and laboratory differentiation between relapse and non-relapse groups.

INTRODUCTION:

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer.[1-5] In high-income countries (HICs), ALL can be successfully treated with approximately 80-90% of children.[2,3] Unfortunately, the cure rate of ALL in low and middle-income countries (LMICs) is still less than 35%.[2,3] Outcome of pediatric cancer therapy at the reference center hospital in Indonesia was still unsatisfactory.[3,4] Relapse is the primary cause of childhood ALL's 15-20% treatment failure.[6] The reemergence of leukemia after undergoing therapy refers to a relapse event.[4,7] The classification of relapse can be based on time, including early, early, and late relapse, and based on the site, such as in bone marrow and extramedullary, including CNS or testicular relapse.[7-9] Relapse is associated with worse outcomes if involving the bone marrow.[5,7]

Over the last two decades, the relapse rates in HICs reported in 15-20%,[10-15] while in LMICs are higher at around 18-41%.[16-20] Efforts to prevent relapse are essential as the prognosis for relapsed ALL is poor. The predictor for relapse is treatment-dependent. Thus it may significantly change in different protocols or with different health systems and socio-economic status.[5] The risk of relapse can be estimated based on some clinical and laboratory results and biological features. Previous studies reported some clinical features, including age, sex, leucocytes count, race, hemoglobin, platelet count, degree of organomegaly.[5,21] At now, there is an improved understanding of

biological features of ALL patients that can predict the treatment outcome, such as immunophenotype and cytogenetical abnormalities.[5,10,21] However, this cytogenetic profile cannot be done in most developing countries due to limited facilities. Moreover, early treatment response can be identified by evaluating the persistence of blasts in the peripheral blood or bone marrow or with minimal residual disease (MRD) observation.[5,21]

The treatment results of childhood ALL with relapse could determine any possible prognosis factors affecting the patient's outcome.[5] However, there are limited studies regarding the characteristics of relapse of childhood cancer in Indonesia. Therefore, this study will describe the clinical and induction remission outcome features known to predict relapse risk in children with ALL using data profiles from the Indonesian Pediatric Cancer Registry (IP-CAR) and Hospital Information System. It is essential to define some characteristics that can be used to allocate patients with a high risk of relapse to targeted therapy, thereby improving survival and outcome of the treatment.

MATERIALS AND METHODS

This retrospective study data was taken from the Pediatrics Hematology-Oncology Unit of a reference center hospital in Indonesia and Indonesia Pediatric Cancer Registry (IP-CAR) in 2018. This research study was affirmed by The Research Ethics Committee Universitas Padjadjaran Bandung No 840/UN6.KEP/EC/2020 and The Health Research Ethics Committee, RSUP, Dr. Hasan Sadikin, Bandung No LB.02.01/X.2.2.1/22546/2020. The subjects used in this study were the patients aged 0-18 who were newly diagnosed ALL at the 2018 period. The monitoring time of this study was until the 30th of December 2020. The number of subjects was determined by a total sampling method with inclusion criteria all patients diagnosed with ALL according to the results of bone marrow sample during 1st—31st of January 2018 who completed the induction treatment and exclusion criteria patients refused chemotherapy, abandonment of and death during treatment. Abandonment of treatment was described as the failure to continue scheduled treatment ≥ 4 weeks

consecutively.[4,7] Among 78 data collected, 35 subjects met the inclusion criteria. We assessed the clinical and induction remission outcome features as relapse predictor outcomes in children with ALL reported from previous studies. Informed consent of patients was waivered.

Initial white blood cells amount in the patient's body and classified into two groups based on the risk stratification in national protocol treatment 2013; <50.000/mm^3 and ≥50.000/mm^3.[22] The risk was stratified according to the ALL treatment protocol 2013 in Indonesia, which divided into standard risk (SR) and high risk (HR) based on age, number of leucocytes, and treatment response.[22] The patient were included in HR when they met one of these criteria: age <1 year or > 10 years, leukocytes ≥50,000/mm^3, the presence of a mediastinal mass on imaging examination, the existence of cell infiltration in CNS and testes, type ALL T cells, bad seven days steroid response.[22] Nutritional status is categorized into normal and malnutrition based on WHO growth chart. Children with standard deviation (SD) > -3 SD - < +2 SD considered as normal. While underweight (weight for age <-2SD), stunting (height for age <-2SD), wasting (weight for height <-2SD), overweight (weight for height >+2SD) are all considered as malnutrition.[22] The French American British (FAB) used for bone marrow morphology classification with a score from 0 to +2 is classified as L1, and -1 to -4 is classified as L2.[22]

Bone marrow morphology was re-examined every the end of the phase to evaluate the success of induction phase chemotherapy and classified into complete remission (<5 lymphoblasts), partial/incomplete remission (5-25% lymphoblast), and no remission (>20% of the 200 nucleated cells in the bone marrow aspiration examination).[22] In this study, we included partial/incomplete remission as no remission group according to national protocol 2013 used in Hasan Sadikin Hospital at 2018 period.

Relapse was indicated by the return of ALL in patients who have already undergone therapy.[4,7] We only observed relapse, which is classified as bone marrow relapse. The criteria were the presence of leukemic cells in more than 20% of the

200 nucleated cells in the bone marrow aspiration examination. The results of peripheral blood tests show the presence of leukemic blasts.[22] According to the children's oncology group (COG), we classified three stages of relapse, including 'very early' relapse that occurs at least 18 months from diagnosis, 'early' relapse between 18 and 36 months from diagnosis, and more than 36 months was called 'late' relapse.[9,22] The procedures followed the ethical standards of the responsible committee on human experimentation (institutional or regional) and the Helsinki Declaration of 1964, as revised in 2013.

Statistical Analysis

Data that fulfill the criteria were presented descriptively and analyzed using SPSS 25 (IBM Corp., Armonk, NY, USA) and Microsoft Excel. Chi-square tests were used to elaborate the association between relapse and sex, leukocyte count, morphological classification, risk stratification, nutritional status. Kruskal Wallis tests were used to elaborate on the association between relapse, age, and induction duration. P-value < 0.05 was considered statistically significant.

RESULTS

During the 2018 period, there were 78 patients newly diagnosed with acute lymphoblastic leukemia (ALL) in the Pediatrics Hematology-Oncology Unit of a reference center in Indonesia. The study's flow chart is illustrated in Figure 1. Of these 78 patients, 43 patients were excluded. Refusal to chemotherapy occurred in 9% of patients, while 7,7% abandoned the treatment. Only 2,6% of patients did not achieve remission, and death during treatment occurred in 35,9% of patients generally because of sepsis and cranial abscess. The remaining 35 patients who received remissions after the completed induction phase were analyzed (**Figure 1**).

Table 1 documents the characteristics of the total subject analyzed in this study. Our data obtained a higher proportion of males 21/35 compared to females. The youngest patient was 1 year old, and the oldest was 16 years old. Among 35 patients, one patient had the highest leukocyte count, which is 267000/mm^3,
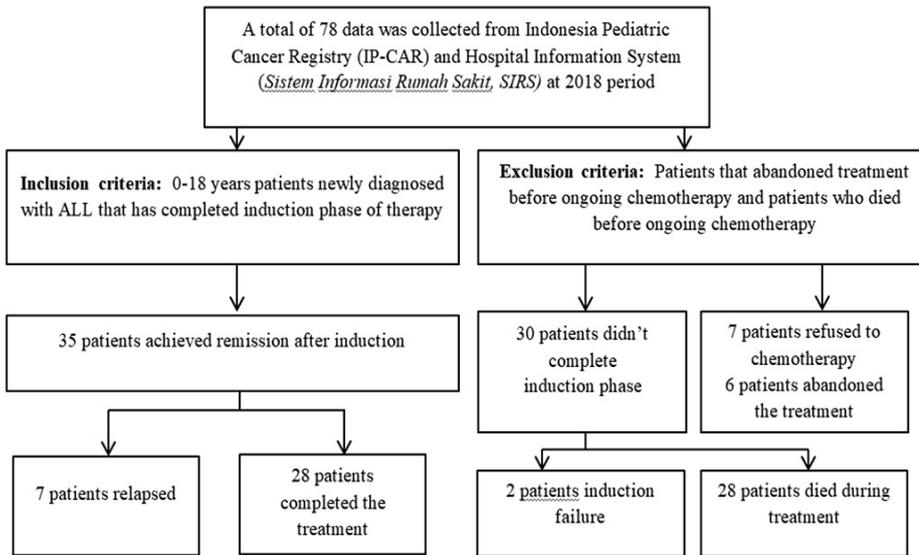
Figure 1. Flow Chart of The Study

Tabel 1. Characteristics of Relapse Event based on Clinical Features

Clinical Features	ALL (n=35)			
	Studied Patients	Non-relapsed ALL patients n=28	Relapsed ALL patients n=7	p value
Age				
• Median (range)	3 (1-16)	3 (1-14)	8 (2-12)	
Age group				0.357
• <10 years	25	21	4	
• ≥10 years	10	7	3	
Sex				
• Male	21	17	4	0.865
• Female	14	11	3	
Leukocytes count				
• <50.000/mm^3	28	22	6	0.677
• ≥50.000/mm^3	7	6	1	
Risk Stratification				
Standard Risk (SR)	19	15	4	
High Risk (HR)	16	13	3	0.867
Nutritional Status				
Normal	21	15	6	
Malnutrition	14	13	1	0.126
Bone Marrow Morphology (FAB)				
L1	11	10	1	
L2	21	17	5	0.370
L3	2	1	1	
Duration of induction (days)				
• Median (range)	100 (60-183)	103 (60-183)	114 (77-176)	0.201

with the lowest is 1020/mm^3. Meanwhile, 19 patients were categorized as the standard risk.

Nutritional status, bone marrow morphology based on FAB, and post-induction outcome are also a consideration to specify the patient's characteristic which relapse occurred. We identified that the standard nutritional status group was a higher proportion. The highest number was classified as L2, and L3 patients were the rarest on the FAB classification.

After completing the induction phase treatment, 35 patients received remission, and seven experienced a relapse. The different characteristics based on clinical features are shown in Table 1 between relapsed and non-relapsed patients. The median duration of induction among relapsed patients was 114 days. Higher relapse cases were documented in the standard risk category with four patients and the normal nutritional status category with six patients. However, the association between relapse event and age, sex, leukocyte count, risk-stratification, nutritional status, and duration of induction showed as insignificant.

As the data are shown in Table 2, all seven patients experienced relapse within less than 18 months, calculated from the initial diagnosis to evaluation after treatment. Specifically, all of them experienced a relapse in the maintenance phase.

A higher proportion of deaths occurred in males, leukocyte count ≥50.000/mm^3, stratified as high-risk patients, and malnutrition group. The youngest patient was 1 year old, and the oldest is 16 years old. Most of the patients died due to infections such as abscess frontalis, sepsis, and disease-related complications.

DISCUSSION

Our study reported that relapse occurred in seven of the 35 patients (20%) who achieved remission, which appear to be in keeping with the relapse rates in HICs compare to other studies from LMICs. They reported higher relapse rates of 21.5%, even up to 58.5%.[16-18] This may be due to the high incidence of death during treatment in this study (35.9%) and treatment abandonment; thus, only several patients completed all

Table 2. Time Point of Relapse Patients

Patients	Time from Initial Diagnosis to Relapse (months)	Treatment phase
Patient 1	4	Maintenance
Patient 2	2	Maintenance
Patient 3	3	Maintenance
Patient 4	5	Maintenance
Patient 5	2	Maintenance
Patient 6	3	Maintenance
Patient 7	6	Maintenance

chemotherapy phases. The characteristics of severe patients, high prevalence of drop-out patients, missed therapy schedule, and side effects of chemotherapy contribute to relapses that lead to most failure of therapy's treatment outcome and toxicity.[3,4] Moreover, in these resource-poor countries, treatment abandonment is a complex and multifactorial phenomenon.[2] The rates in LMICs may vary from 16 to 50%.[3] Although there is a reduction compared to the previous study in Indonesia (25%), the patients who refused or abandoned the treatment results remain high (17%). Financial problems, transportation difficulties, lack of essential drugs and medical facilities, also psychological reasons such as fears and specific beliefs about ALL curability should all be addressed to prevent the refusal or abandonment of treatment.[3]

Over the years, several efforts have been made to classify and identify some clinical indicators that respond poorly to therapy.[5,10,21,23] However, in our study, the clinical characteristics such as age, sex, leukocyte count, risk stratification, FAB morphology classification, nutritional status, and duration of induction have no significant difference to relapse event. This result is the same with research in Makassar[24] and Jakarta[25] that age did not influence relapse. Previous studies by also reported that sex did not influence relapse.[25,26] These findings probably indicated that in LMICs, age and sex are merely representative markers that reflect differences in several other factors such as a different molecular subtype of ALL, immunological, or behavioral factors, thus needing further research.[20,21] The higher number of patients in this study had a leukocyte count less than 50.000/mm³ in the relapse group because most patients

with WBC≥50.000/mm³ died during initial induction. ALL patients in childhood, when diagnosed, have a significantly lower survival rate and are associated with early morbidity and mortality due to microcirculatory hyperviscosity and leukostasis.[27-29] Along with a study by Vaitkeviciene et al., which reported high leukocyte count was independently and significantly associated with risk of early death.[27] Moreover, the research conducted in Dr. Soetomo General Hospital Surabaya reported that nutritional status is not associated with relapse but contrary with the ALL children mortality.[30]

Zhang reported that patients at high risk tended to relapse and had a worse prognosis.[31] Our study shows that relapse was common in patients at standard risk with a total of four cases compared to high risk with 3 cases, although not statistically significant. The explanation of that finding is probably because many high-risk patients were excluded due to death during ongoing treatment. This result might be indicated that current schemas of risk-stratified therapy remain imperfect and may be imprecise. Many patients categorized as low-risk experienced relapse due to inadequate therapy, while the high-risk patients were treated more intensively than standard for the cure, leading to toxicity and death.[21] Research conducted on Mexican children showed that most populations were high-risk groups (HR). However, interestingly there was a protective effect in this group (RR 0.83, 95% CI 0.5-1.4) which supports our study.[16] Thus, we suggest reallocating the risk-stratified therapy. According to several studies, if the availability of precise data such as molecular biology or cytogenetic is difficult in a developing country, intermediate risk as the third

classification based on minimal residual disease (MRD) determined by two times polymerase chain reaction (PCR) may be needed. However, although MRD is currently the most powerful prognostic factor for childhood cancer, half of all relapses on Children's Oncology Group (COG) trials regarding ALL occur in patients group with excellent early MRD response.[21] Thus, further works to predict which children are at the highest risk for relapse are needed. Reclassify the risk into intermediate risk, another high risk, and very high-risk patients based on the addition of its personalized cytogenetic and molecular may be promising for a better outcome.[21]

Our subjects' average duration to achieve remission was more than seven weeks, which is not following the national treatment protocol of ALL in childhood which is expected to be achieved for 42 days.[8] As is well known from the literature, prolonged use of steroids can suppress the secretion of adrenocorticotropic (ACTH) by the pituitary gland and corticotrophin-releasing hormone (CRH) by the hypothalamus resulting in secondary adrenal cortical atrophy.[32] A study in Iran reported that 17 patients (41.4%) experienced adrenal suppression due to prolonged glucocorticoid use with symptoms such as fever, lethargy, nausea, headache, and even bradycardia and fall in blood pressure. This report might be an issue as tapering off the steroids still results in prolonged use.[32] Thus, the risk of relapse should also be weighed for selecting the type and dosage of glucocorticoid as the relative efficacy of these drugs is dose-dependent and must be carefully used against toxicity.[29]

In order to prevent relapse, childhood ALL who achieved remission require a maintenance therapy phase for about two years that includes oral chemotherapy.[8] Two drugs commonly used are 6-mercaptopurine (6-MP) and methotrexate (MTX) which can be administered orally by the patients, caregiver, or parents.[8,33] Unfortunately, the data we obtained in our study shows that all seven patients were categorized as a very early stage of relapse, which happened in less than 18 months. According to some studies, patients who relapse in the earlier

stage were less likely to survive than those in the late stage.[9,21,22] The characteristics of higher risk of ALL patients contribute to very early relapses, which lead to most failure of the treatment outcome and toxicity of therapy.[3,4] Moreover, all relapse events occurred in the maintenance phase (Table 2). The possible explanations of this finding are first. However, ALL protocols recommend the doses to be adjusted to a target WBC level with the evidence that lower WBC is related to reduced risk of relapse. Some patients with high WBC did not receive higher doses of 6-MP/MTX.[6,33] In addition to the lack of essential drugs in LMICs, this is probably because the toxicity of the treatment during the earlier phase of maintenance therapy could reduce the physician compliance to treatment intensification.[6] Second, since patients who achieved remission become practically asymptomatic but remain under complex and extended therapy, non-adherence of treatment during the maintenance phase is somehow expected. It could be challenging to raise family awareness to follow the treatment in the maintenance phase for specific communities and ethnic groups.[34] It was estimated that 18-25% of children in remission of ALL are missing medication intake at least once during the early eight weeks of the maintenance phase.[6,34] Several studies reported that poor patient adherence to the prescribed oral doses of 6MP or MTX had been significantly associated with a higher risk of relapse.[6,33-35] Third, the individual variations to produce 6-MP metabolites which influence erythrocyte thioguanine nucleotide (TGN) levels due to the varying dose intensity and interruptions of drugs is also related to the risk of relapse between adhere and non-adhere patients.[6,33] Non-adhere patients tend to have varying TGN level then increases the risk of ALL relapse.[33] Thus, complex interventions are required to improve treatment adherence.

There are few limitations in this study. First, this is a retrospective descriptive study from a single institution. The data evaluated during this study might not significantly represent real conditions due to the small subject and many patient data that are missing or not available. Second, the descriptive data might not determine a clear association between the variables and the relapse event.

CONCLUSION

This study found that all the relapse events occurred in the very early stage, which is in the maintenance phase. However, there is no significant demography, clinical, and laboratory differentiation between the relapse and non-relapse groups. The higher rate of standard risk group relapsed on this study and the high amounts of induction deaths related to infection/sepsis indicated that efforts to redefine the group with the highest risk for unfavorable outcomes are essential. Further research on ALL patients' biological features that can predict more precisely, such as immunophenotype and cytogenetical abnormalities, are also needed for more reliable predictors of outcome.

Key Messages: The high number of relapse patients in the very early phase and only 45% of patients who achieved induction remission indicated a considerable need to improve the treatment protocol and supportive treatment during the induction phase and redefine the group who has the highest risk for unfavorable outcome.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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