

Early Steroid Response is the Prognostic Factor of Remission in Children with Acute Lymphoblastic Leukemia during Induction Phase Chemotherapy

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Received July 29, 2019; Accepted August 02, 2019; Published February 26, 2020

ABSTRACT

Introduction: Acute Lymphoblastic Leukemia (ALL) as the most common type of cancer in children has a high cure rate with chemotherapy treatment. The incidence of induction phase remission was found to be directly proportional to the overall success of ALL treatment. The initial steroid response to the induction phase of chemotherapy is thought to have a prognostic role in ALL treatment.

Objective: To determine the initial steroid response as a prognostic remission factor in ALL children during induction phase chemotherapy treatment using the 2013 ALL National Child Protocol.

Materials and methods: An observational analytic study with a prospective cohort design at Sanglah Hospital, Denpasar, since May 2017 until the sample study has reached. The study was conducted data from medical records. Children with ALL will enter the stage of the initial steroid induction phase for the first 7 days. On the 8th day, a blood smears examination done to evaluate the steroid response. Children grouped as positive blast and negative blast. They prospectively observe during induction phase for the remission.

Results: Of the 39 children with LLA, 23 subjects had good responders and 16 subjects were poor responders. From both, 31 subjects were remission and 8 subjects were not remission. Bivariate analysis showed that the initial steroid response was associated with the induction phase remission (RR=1.46 (95% CI 0.98-2.18), p=0.03).

Conclusion: This study proves that there is a relationship between the initial steroid response and the occurrence of the induction phase remission.

Keywords: Acute lymphoblastic leukemia, Initial steroid response, Remission

INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) as the most common type of cancer in children has a high cure rate with chemotherapy treatment [1]. The incidence of induction phase remission was found to be directly proportional to the overall success of ALL treatment [1,2]. The initial steroid response to the induction phase of chemotherapy is thought to have a prognostic role in ALL treatment [3]. This study conducted to prove the initial steroid response as a prognostic remission factor in ALL children during induction phase chemotherapy treatment using the 2013 ALL National Child Protocol.

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Citation: Putri Y, Widnyana AANKP, Bikin Suryawan IW, Arimbawa IM, Hartawan NB, et al. (2020) Early Steroid Response is the Prognostic Factor of Remission in Children with Acute Lymphoblastic Leukemia during Induction Phase Chemotherapy. Chemother Res J, 2(1): 38-43.

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MATERIALS AND METHODS

An observational analytic study using a cohort design was conducted at the Sanglah Hospital, Denpasar. Samples were selected with consecutive sampling. The inclusion criteria included ALL patients undergoing hospitalization and taking chemotherapy treatment at Sanglah Hospital and passing the treatment period of the induction phase to completion; age of >1 month to 18 years old when the study was conducted. Exclusion criteria included patients or parents or guardians of patients refuse to participate in the study. Estimation of the samples was determined by unpaired categorical samples formula. Given that this study was a prospective study and considers the risk of drop out from the sample studied, the addition of samples from the calculation of the drop out of 5% was applied and found that the total samples in this study were 38 samples.

Acute lymphoblastic leukemia (ALL) confirmed by examination of bone marrow aspiration (BMA) with the discovery of blast >30% in the bone marrow. Children are those aged 18 years and under. Good Responder was a sample with negative blast results based on evaluation of peripheral blood smear on day 8 after an ALL patient received 7 days of steroid therapy, which is a nominal variable divided into yes=1 and no=2. Drop out was the patient with his own will or the parent/guardian wants to stop or leave the hospital before the treatment of ALL chemotherapy were ends. The age at diagnosis is determined based on chronological age (according to date of birth) obtained from parents or guardians. The initial leukocyte count is the number of leukocytes when the first child comes with clinical symptoms that lead to leukemia, obtained from the results of hematological examination (complete blood), stated as a leukocyte count >50,000 cells per mm³ and <50,000 cells/mm³. Induction phase chemotherapy is the initial stage of chemotherapy for newly diagnosed ALL patients. Includes administration of dexamethasone or prednisone for the first seventh days accompanied and followed by administration of other chemotherapy drugs according to the 2013 National ALL Protocol for children. Remission was a condition with the amount of blast less than or equal to 5% in the bone marrow (via BMA examination) at the end of the induction phase chemotherapy treatment (+ 7 weeks), which is a nominal variable with 1=yes and 2=no. Risk stratification is the grouping of ALL patients. Standard risk if the initial leukocytes are diagnosed <50,000 cells/mm³. High risk if leukocytes >50,000 cells/mm³. The

type of steroid used is the selection of steroids that are used during the induction phase of the chemotherapy. The initial induction phase is the 0th week of the induction phase chemotherapy. The duration of the induction phase is the duration of each sample to complete the induction phase chemotherapy. Differentiated into 7 weeks, >8 weeks and not finished (died).

The data obtained were analyzed using a computer program for univariate, bivariate and multivariate analysis. The relationship between variables was analyzed and presented using X² to determine the significance of the comparative hypothesis of two unpaired categorical samples. Relationships are considered statistically significant if p<0.05. This research was conducted based on the ethical feasibility from the Research Ethics Committee of the Faculty of Medicine Udayana University, Sanglah Hospital Denpasar No.743/UN.14.2/KEP/2017.

RESULTS

This research was conducted since May 2017 until samples were fulfilled. There were 44 children with an LLA diagnosis during the study period. Of the 44 children who met the inclusion criteria, two subjects were excluded because they were approved. The subjects were subsequently treated with early-stage steroid chemotherapy induction according to the 2013 LLA National Child Protocol in accordance with the risks then continued with the 8th day blood smear examination phase of initial induction with steroids. Based on the results of the examination, the subjects were divided into good respondents and poor respondents. There were 26 subjects in the good respondent group and 16 subjects in the poor respondent group. The two groups then discussed the therapeutic phase according to the protocol. During the treatment period, 3 subjects were dropped out. The subjects were then observed and followed up until the induction phase ended. At the end of the induction phase, it was obtained from 23 subjects in the group of respondents who were good, 21 subjects were remission and 2 subjects were not remission. While from 16 subjects in the poor respondent group, 10 subjects were remission and six subjects were not remission.

The basic characteristics of the study subjects based on the initial steroid response are shown in **Table 1**. The data in the table shows that the most subjects were children in the age group 1-10 years (24 subjects, 77.4%).

Table 1. Subjects characteristic.

Characteristics	Remission	
	Yes (n=31)	No (n=8)
Age group. n (%)		
1-10 years	24 (77.4)	4 (50.0)
>10 years	7 (22.3)	4 (50.0)
Gender. n (%)		
Male	12 (38.7)	5 (63.0)
Female	19 (61.3)	3 (37.5)
Region. n (%)		
Bali	21 (67.8)	6 (75.0)
Outer Bali	10 (32.3)	2 (25.0)
Initial WBC count. n (%)		
≤ 50.000	26 (83.8)	4 (50)
>50.000	5 (16.3)	4 (50)
Risk stratification. n (%)		
Standard risk	17 (73.9)	0 (0.00)
High risk	14 (26.0)	8 (100.0)
ALL type. n (%)		
ALL 1	9 (29.0)	2 (25.0)
ALL 2	22 (70.9)	6 (75.0)
Induction phase length, n (%)		
7 weeks	13 (42.0)	0 (0.00)
>8 weeks	18 (58.1)	0 (0.00)
Unfinished died	0 (8.7)	8 (100.0)

Based from gender, most subjects were female, with the majority of subjects being male (63%) in the group not remission. Judging from the response to the initial steroid induction phase, the male sex was more in the Poor Responder group (56.2%). As many as 69.2% of the subjects came from Bali, with dominance from the Denpasar area, while in subjects from outside of Bali, West Nusa Tenggara (NTB) was the largest area of origin for outside Bali. Judging from the risk stratification, 74% of the Good Responder group is included in the risk standard stratification, while the Poor Responder group is all high risk. All samples in the standard risk group experienced remissions. Most subjects were ALL type 2 ALL, both in the remission group and in the non-remission group. Judging

from the duration of completing the induction phase, as many as 58.1% of subjects completed the induction phase >8 weeks, 42% of subjects completed the induction phase within 7 weeks and there were 8 subjects who could not complete the induction phase due to death. Of the 8 dead subjects, the causes of death included intracranial bleeding, disseminated intravascular coagulation (DIC), pneumonia with respiratory failure and septic shock.

The relationship of the initial steroid response with the induction phase remission was analyzed bivariately with X^2 . The results of bivariate analysis are shown in **Table 2**. Based on **Table 2**, it can be seen that the initial steroid response was related to the induction phase remission. Most subjects

experience remission. The difference was statistically significant (RR=1.46 (95% CI 0.98-2.18), $p=0.03$).

Table 2. Relationship of initial steroid response induction phase and remission.

	Variables	Remission		RR	CI 95%	p value
		Yes	No			
Good Responder	Yes	21 (91.3%)	2 (8.7%)	1.46	0.98-2.18	0.03
	No	10 (62.5%)	6 (37.5%)			

Multivariate analysis was performed to determine the pure relationship between the initial steroid response and remission after calculating confounding variables. The variables included in the multivariate analysis included the initial steroid response, age, sex, initial leukocyte level (Table 3). Based on the results of multivariate analysis of the variables of good responder, age, sex, and initial

leukocyte levels, it was found that there was a tendency for a clinically strong relationship between good responder and the incidence of remission (OR=6.26 (95% CI 0.88-44.4), $p=0.06$) although statistically the difference is not significant. Variables of age, sex and initial leukocyte levels did not have a significant relationship with the incidence of remission.

Table 3. Multivariate analysis of the relationship between good responder, gender, age and initial WBC count with remission.

Variables	OR	CI 95%	p value
Good responder	6.26	0.88-44.4	0.06
Age	1.03	0.84-1.25	0.78
Gender	0.67	0.10-4.23	0.67
Initial WBC count	0.98	0.97-1.00	0.11

DISCUSSION

The results of this study prove that the initial steroid response (good responder) increased remission in induction phase LLA chemotherapy by 1.46 times with statistical significance that was significant ($p<0.05$). Meaningful association size in this study can be explained as a positive relationship between the prognostic factors of the initial steroid response and the incidence of remission with relative risk 1.46 times more likely in the good responder group to experience remission compared to the poor responder group. This significance is supported by a fairly narrow range of confidence intervals (IK) from 0.98-2.18. But as an estimate in the population it appears that the value of the confidence interval includes number 1 which shows that in small samples with varied data, equalization measures have been carried out by the computer to see the distribution of the overall data. The IK range means that if this research is carried out again in the same way, it is believed that in the population, the relative risk value will be 0.98 to 2.18 times in the good responder group compared to the poor responder group in increasing the chemotherapy induction phase remission pediatric patients with LLA [4,5].

The role of steroids in LLA treatment is based on theory in a study by Inaba et al. [3] and Shah and Kumar [6] who explained that glucocorticoids have cytotoxic or lympholytic effects mediated by binding to glucocorticoid receptors in

the cytoplasm. As a result of this bond, glucocorticoid receptors will undergo homodimerisation, translate into the nucleus and then interact with glucocorticoid response elements to transact gene expression or can also remain monomeric and suppress the activity of transcription factors such as activating protein-1 (AP-1) or nuclear factor-kB (NF-kB). Both of these processes inhibit cytokine production, change the expression of various oncogenes and induce cell cycle cessation and apoptosis.

The results showed that 74% of the Good Responder groups were included in the standard risk stratification, while for the Poor Responder group, all were high risk. Judging from gender, the Poor Responder group was dominated by 56.2% with male sex. This finding is in accordance with the research [6,7] which explain that to be able to cause cytotoxic or lympholytic effects, steroids need to bind to their receptors in the cell cytoplasm called glucocorticoid receptors. It was found that the number of receptors on leukemia cells will affect their sensitivity to steroid work. The fewer the number of receptors, the lower the response (poor responder). The working ability of these receptors added by Oakley and Cidiowski [7] is very closely related to the molecular structure of each of these receptors, the signal pathway that is traversed, and includes molecular connecting proteins. In this study no assessment of the number of receptors was carried out. On the other hand, in line with the

results of this study, Shah and Kumar [6] explained in his journal that there are several factors that increase the tendency of poor responders to induce remission failure including male sex and high initial leukocyte counts. Different remission rates in the group of good responder and poor responders in this study besides being influenced by the above factors may also be caused by the type of steroids obtained in accordance with the risk-based chemotherapy protocol. The 2013 LLA National Child Protocol used in this study provided prednisone as an initial induction therapy in the standard risk and dexamethasone groups in the high risk group.

Other studies regarding the role of treatment response, specifically the initial steroid response to the incidence of induction phase remission were carried out by Widjajanto et al. [8] and Vaghela et al. [9]. Widjajanto et al. [8] found in a prospective study of 165 new LLA patients who later received protocol-based chemotherapy which was subsequently observed and analyzed the effect of response to initial steroid treatment as an important prognostic factor in the treatment of LLA patients. It was found that 117 patients from 165 patients (70.9%) experienced complete remission. Namely 15 out of 32 patients were poor responders (46.9%) and 102 of 133 patients (76.7%) were good responder with $p < 0.01$. Research by Vaghela et al. [9] in India revealed that patients with negative blasts had a 2 year chance free survival opportunity of 76.1% compared with positive blast with an opportunity of 53.3%. Prednisone Good Responder is said to have a 71.42% 2 year event free survival opportunity. Meanwhile research by de Sousa et al. [2] obtained similar results which revealed that patients who experienced complete hematological remission and no early relapse were good responder therapy for induction phase but with more specific examination showed the level of negative blast in question was marked with lymphoblast levels $< 1000/uL$ in 8th day peripheral blood smear examination. Similarly, research by Wei et al. [10] through a retrospective study of 74 patients by adding the specifications on immunophenotyping of lymphoblast in question, namely that at T-LLA only < 15 years of age from January 2003 to December 2012 were analyzed for the effect of response to initial treatment with prednisone as a prognostic factor. It was found that Prednisone Poor Responder was closely related to an increase in induction failure (14.8%) and a decrease in survival rate (5 year event free survival 5.11%).

The results of multivariate analysis were also conducted in assessing the relationship between good responder and the occurrence of induction phase remission in LLA chemotherapy by controlling other variables which were considered as prognostic factors from the literature. The results show that there is a tendency for a clinically strong relationship between good responder and the incidence of remission of 6.26 times, so that it can be clinically said that this study is very important because clinically, the relative risk value is more than 2 [4]. Statistically the difference was

not significant and with the results of a wide confidence interval indicating that the likelihood of remission in the population could be comparable in both groups by 6%. This can occur because the sample of this study is small with varying data and wide data distribution so that the size of the association that is meaningful in this study is not followed by good estimation precision [4,5]. The occurrence of remission in children with LLA during induction phase chemotherapy, in addition to being associated with the initial steroid response is also influenced by several other factors referred to as prognostic factors. These factors include age at diagnosis, sex, initial leukocyte count and LLA subtype as found in the study conducted by de Sousa et al. [2] that the age of one to nine years with an initial leukocyte count $< 50,000$ cell/L is said to be a prognostic factor that supports the occurrence of remission. While in the study by Simanjorang et al. [11] found that male sex served as a bad prognostic factor for the occurrence of remission because it increased the risk of death 3.03 times in LLA patients. In contrast to these findings, data from age, sex and initial leukocyte counts were not found to be significantly different between the two groups. This finding is similar to that obtained by Permatasari et al. [12] that there were no differences in the incidence of remission in groups of women and men. Meanwhile Perdani et al. [1] in his study of hematological parameters with the incidence of remission showed that the initial leukocyte levels did not have a statistically significant effect on the induction phase remission. These differences in results can occur due to differences in the size of the sample studied including also the distribution and variation of data in each study [4,5].

CONCLUSION

This study proves that there is a relationship between the initial steroid response and the occurrence of the induction phase remission.

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