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Correlation between Nutritional States with Hematological Toxicity in Children with Acute Lymphoblastic Leukemia

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A B S T R A K

Status gizi pada anak dengan *acute lymphoblastic acute (*ALL) diketahui dapat mempengaruhi efek samping yang mungkin timbul setelah dilakukan kemoterapi. Salah satu efek samping yang sering terjadi pada anak dengan ALL pasca kemoterapi adalah *hematological toxicity. Hematological toxicity* adalah efek toksik yang ditimbulkan dari obat kemoterapi yang menyebabkan gangguan pada sel darah yang bila tidak diatasi dengan baik dapat menimbulkan kematian. *Hematological toxicity* sering terjadi pada anak ALL pasca kemoterapi namun belum menjadi perhatian tenaga kesehatan terutama perawat. Tujuan penelitian ini adalah ingin mengetahui hubungan antara status gizi dengan *hematological toxicity* pada anak ALL yang sedang menjalani kemoterapi. Penelitian ini dilakukan di RSUP Dr Hasan Sadikin Bandung pada bulan Desember 2016 dengan metode penelitian korelasi dengan pendekatan retrospektif. Penelitian ini dilakukan pada 198 responden yang diambil dari catatan rekam medis bulan Januari-Juli 2016 dengan menggunakan purposive sampling. Analisa data menggunakan uji Korelasi Spearman Rank (Rho). Hasil penelitian didapatkan 13 dari 17 responden berstatus gizi sangat kurus mengalami hematological toxicity dan terdapat hubungan yang signifikan antara status gizi dengan *hematological toxicity* pada anak ALL (p=0,015) dengan korelasi yang sangat lemah (r=-0,172). Kesimpulan: Terdapat hubungan antara status gizi dengan *hematological toxicity* pasca kemoterapi pada anak LLA yang menjalani kemoterapi. Oleh karena itu, pentingnya pengkajian status gizi dan monitoring tanda-tanda *hematological toxicity* untuk mencegah terjadinya efek buruk akibat dari pengobatan kemoterapi pada anak dengan ALL.

Kata kunci: Anak, *Hematological toxicity*, Kemoterapi, Leukemia, Status gizi

A B S T R A C T

Acute lymphoblastic leukemia (ALL) is the most common cancer in children and one of the leading causes of death in children. Many factors affect the prognosis of acute lymphoblastic leukemia, one of which is the nutritional status. Nutrition status in children with acute lymphoblastic acute is known to affect side effects that arise after chemotherapy. One of the side effects which often occur in children with ALL post chemotherapy was hematological toxicity. Hematological toxicity was one of the side effect chemotherapy if not treated properly can caused death. The aimed of this research was to analyze the correlation of nutritional status with hematological toxicity on children with ALL in chemotherapy. This study was done in Hasan Sadikin General Hospital in Bandung in December 2016 with correlational research was performed with retrospective approach. 198 respondents were selected using

purposive sampling taken from medical records during January-July in 2016. Data was analyzed using Spearman Rank Correlation Test (Rho). The study showed that 17 children with ALL were categorized in very thin (86,7%) suffered from hematological toxicity thus discovered significant correlation between nutritional status pre chemotherapy and hematological toxicity post chemotherapy in children with ALL (p=0,015) for a very weak correlation (r=-0,172). The conclusion in this study researched was that nutritional stated chemotherapy was correlated with hematological toxicity after chemotherapy in children with ALL. Therefore, assessment of nutritional status in children with acute lymphoblastic leukemia should be done especially when chemotherapy treatment is being taken to minimize the occurrence of hematological toxicity.

Key words: *Children, Leukemia, Chemotherapy, Hematological toxicity, Nutrition state*

INTRODUCTION

Cancer in children is one of the health problems in the world. Although the incidence of cancer in children is quite rare that was 1% in the world. But it is one of the main causes of death of 80,000 children (ages 0-14 years) in 2012 (American Cancer Society, 2015). Cancer in children consists of various types, but the most common cancer in children 30-40% is acute leukemia especially acute lymphoblastic acute (ALL) (Kementerian Kesehatan RI, 2011).

Many methods of treatment to increase the life expectancy of children with acute lymphoblastic leukemia. One of the main treatments is chemotherapy (Wong, Eaton, Winkelstein, Wilson, & Schwatz, 2009). Chemotherapy is an effective treatment for acute lymphoblastic leukemia in Indonesia. But each child has a different reaction when they in this treatment. Side effects from chemotherapy are sometimes more severe than the symptoms of leukemia. One of the side effects that often occur after chemotherapy is myelosuppresion (the suppression of bone marrow activity) resulting in the emergence of hematological toxicity (Metha & Hoffbrand, 2012).

Hematological toxicity is one of the main side effects of chemotherapy drug administration that occurs due to myelosuppresion that can inhibit the development of normal blood stem cells where white blood cell count, red blood cells and platelets are disrupted (Cancer Agency, 2015). Children who undergo chemotherapywith leukemia always experience hematological toxicity. Signs of hematologica toxicity of each child are different such as leukopenia, thrombocytopenia and anemia (Isnani, Perwitasari, Andalusia & Mahdi, 2014). Based on the results of the study that children with ALL who undergoing chemotherapy will experience hematological toxicity but this has not been a concern more by health workers. Whereas hematological toxicity can cause adverse effects on the patient. If not handle immediately may cause infection and bleeding that can eventually cause delayed of treatment or maybe death (Metha & Hoffbrand, 2012; Cancer Agency, 2015).

The factors that influence the occurrence of hematological toxicity according to Cancer Agency (2015) are age, nutritional status, chemotherapy types, type of radiation and bone marrow reserve. Of the five factors, nutritional status is one factor that can be followed better by health workers, especially nurses. Nutritional status became one of the prognoses in children with ALL (Roger, 2014). Nutritional status is associated with short-term and long-term adverse effects after chemotherapy treatment in children with ALL (Owens, Hanson, McArthur & Mikhailov, 2013). In addition nutritional status associated with the occurrence of relapse, increased free survival event (EFS) and the occurrence of treatment related toxicity (TRT) and disability (Orgel, Sposto, Malvar, Seibel, Ladas, et al.,2014; Sari, Windiastuti, Cempako & Devaera, 2010; Alcazar, Enriquez, Ruiz, Gutierrez, & Arangure, 2013). So it is said that the assessment and intervention of nutritional status in children with ALL can improve the quality of life, reduced toxicity and increase survival rate (Hazarika & Dwivedi, 2015).

However, based on other studies, nutritional status has no effect on toxicity, relapse, outcome and early death in ALL patients undergoing chemotherapy (Hijiya, Panetta, Zhou, Kyzer, Howard, et al.,2006).

Differences in the results of this study indicate the need for further research related to this. In RSUP Dr Hasan Sadikin Bandung, the incidence of children with ALL is the most cases of cancer in children in this hospital with the average patient throughout 2016 is + 55 case. Based on data from 2015-2016 it is known that the mortality rate of children with ALL undergoing chemotherapy in Kenanga 2 increased from 3 children in 2015 to 11 children in 2016 (January -July 2016). Based on the observation, it is known that children with nutritional status are less likely to experience hematological toxicity, relapse and even death. Therefore, based on the background of the above problems researchers interested in further analyzing the correlation of nutritional status before chemotherapy with toxicity effects after chemotherapy that is hematological toxicity in children acute lymphoblastic leukemia.

The objectives of this study were to identify the nutritional status of pre-chemotherapy, identify hematological toxicity after chemotherapy and to know the correlation between nutritional status and hematological toxicity in children with acute lymphoblastic leukemia who undergo chemotherapy.

METHOD

This research is a correlational research with retrospective approach. The samples of this study were children with ALL who undergo chemotherapy in the consolidation and maintenance phase during January-July 2016 at RSUP Dr Hasan Sadikin Bandung. Method of data collecting by documentation study by using instrument sheet result of documentation study. Data were taken from medical records consisted of age, sex, chemotherapy phases, nutritional status based on body weight and height of respondentswho then calculated BMI and classified based on *Standar Antropometri Penilaian Status Gizi Anak Kementerian Kesehatan Tahun 2010* and laboratory results to be viewed based on Common Terminalogi Criteria for Adverse Event (CTCAE v3) modifications with toxic criteria (grade 1-5) and non toxic (grade 0). Data analysis used in this research is univariate analysis and bivariate analysis. Univariate analysis to determine the frequency distribution of nutritional status and hematological toxicity. Bivariate analysis using Spearman Rank (Rho) to analyze two variables namely nutritional status with hematological toxicity.

RESULT

Children with ALL in this study were 198 children. The research was conducted on 01-30 December 2016. Based on the characteristics it is known that the male sex is higher than the female ie 59.6% and male 40.4% (1.4: 1). The age of children with ALL who underwent chemotherapy more than half (56.6%) was 1-6 years old and chemotherapy more than half (64.1%) was the maintenance phase.

Nutritional status in children with ALL (n = 198) of pre-chemotherapy almost half (44.9%) was the norm, but there is a small part (7.6%) have very thin nutritional status and a small portion (17.7%) obesity. The incidence of hematological toxicity in children with ALL (n = 198) post-chemotherapy was more than half (64.6%) subjected to hematological toxicity.

Table 1. Distribution of Characteristics of Children with ALL undergoing Chemotherapy January-July 2016 (n = 198)

No	Variabel	f	%
1.	**Gender**		
	Male	118	59,6
	Female	80	40,4
2.	**Age**		
	<1 tahun	1	0,5
	1-6 tahun	112	56,6
	6-11 tahun	51	25,8
	>11 tahun	34	17,2
3	**Phase chemotherapy**		
	Consolidation	71	35,9
	Maintenance	127	64,1

Based on the results of the study it is known that there is a significant relationship between pre-chemotherapy nutrition status with hematological toxicity post-chemotherapy in children with ALL (p = 0.015) with a very weak and negative correlation (r = -0.172).

DISCUSSION

In this study, researchers have reviewed 295 records of medical records in children with ALL undergoing chemotherapy in January-July 2016. But of all medical record records, there are many incomplete medical record records either from weight assessment by doctors or nurses and most of the laboratory results are not included in the medical record so it must be validated using a computer system. The researchers finally obtained 198 medical record records that fit the expected criteria of inkulsi in this study of 295 records of medical records.

Children with ALL who underwent chemotherapy in this study 59.6% were male and 40.4% were female. Various studies suggest that ALL is more prevalent in boys than girls and it is known that male sex has 1.29 times of death (Sulastriana, Muda, & Jemadi, 2012; Hossain, Xie, & McCahan, 2014). Age of children with ALL who underwent chemotherapy treatment in this study 56.6% were aged 1-6 years, 0.5% were age <1 year, 25.8% were age 6-11 years and 17.2 were aged > 11 year. Leukemia disease is common in children over 1 year and its peak occurrence occurs between the ages of 2-6 years (Wong, et al.,2009). Children with ALL diagnosed at 1-4 years of age and immediate intensive chemotherapy treatment will be more likely to survive than at age 0-12 months or children over 4 years of age (Hosan, Xie & McCahan, 2014).

During January-July 2016 it was found that children with ALL who underwent chemotherapy were in the consolidation phase there were 35.9% and in the maintenance phase there were 64.1%. Treatment of chemotherapy in children with ALL consists of three phases consisting of induction, consolidation and maintenance phases. In this study the researchers only take the consolidation and maintenance phase because in this phase the burden of the tumor is low and already in remission so that the resulting laboratory results not due to symptoms of leukemia but due to myelosuppression effects due to chemo-

Table 2. Distribution of Nutrition Status of Children with ALL (Pre-Chemotherapy) January-July 2016 (n = 198)

Variabel	f	%
Very thin	15	7,6
Thin	22	11,1
Normal	89	44,9
Obese	37	18,7
Obesity	35	17,7

Table 3. Distribution of Hematological Toxicity of Children with ALL (Post-Chemotherapy) January-July 2016

Variabel	f	%
Non Toxic	70	35,4
Toxic	128	64,6

Tablel 4. Distribution of Nutritional Status of Pre Chemotherapy with Hematological Toxicity Post-Chemotherapy in Children with ALL January-July 2016 (n = 198)

Variabel	Hematological Toxicity				Total		p value	r
	Non Toxic		Toxic					
	f	%	f	%	f	%		
Nutritional Status								
Very thin	2	13,3	13	86,7	15	100		
Thin	9	40,9	13	59,1	22	100		
Normal	25	28,1	64	71,9	89	100	0,015	-0,172
Obese	17	45,9	20	54,1	37	100		
Obesity	17	48,6	18	51,4	35	100		

therapy treatment.

In this study it was found that nutritional status of children with ALL at pre-chemotherapy 44.9% was normal, 7.6% very thin, 11.1 skinny, 18.7% obese and 17.7% obesity. Nutrition status in children with ALL undergoing chemotherapy treatment experienced changes during treatment and was associated with a phase of chemotherapy treatment that was being undertaken (Wolley, Gunawan & Warouw, 2016). There are several factors that cause malnutrition in children with cancer include tumor-specific factors, factors relating to patients and factors related to treatment (Alcazar, et al., 2013).

Children with ALL with unknown nutritional status are at high risk for relapse and dying compared with children with normal nutritional status and few who can complete the treatment. Children with ALL who have good nutritional status can survive more than 5 years with a presentation of 80%, whereas children with ALL who have less nutritional status there are only 26% who can survive and similar to early mortality and relapse during the first year of treatment, only 4% of patients were diagnosed with good nutritional status experienced early mortality and relapse while 63% of patients diagnosed with poor nutritional status likely to experience relapse or death (Simanjorang, 2012).

The side effects of chemotherapy are sometimes more severe than the symptoms of leukemia itself. One of the side effects of chemotherapy that can cause death is the hematological toxicity (Isnani, et al., 2014). In this study it was found that 64.6% of children with ALL who underwent chemotherapy experienced hematological toxicity post-chemotherapy. Based on the results of the study note that children with ALL who underwent chemotherapy have a tendency to experience hematological toxicity.

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Hematological toxicity is a side effect of chemotherapy in the presence of myelosuppression which causes a disruption in the formation of blood cells resulting in leukopenia are susceptible to infection, thrombocytopenia that cause bleeding and decrease Hb that cause anemia. Children with ALL who experience hematological toxicity in addition to causing death, but the thing that often becomes a problem is long hospitalization. Long hospitalization is due to blood transfusion, antibiotic treatment and leukogen (as a white blood cell enhancer) should be given gradually and may take several days to improve the hematologic value and general condition of the patient. In addition, children with ALL who experience hematological toxicity causes chemotherapy treatment to be delayed and the dose of chemotherapy was reduced (Karch, 2011). According to result of research by Asim, Zaidi, Ghafoor and Qureshi (2011) found that of 74 children with ALL who died during chemotherapy treatment, 63 children died of infection, 8 children died of bleeding and 3 children died of other toxicities from chemotherapy treatment.

In this study it is known that there is a significant relationship between pre-chemotherapy nutrition status with hematological toxicity post-chemotherapy in children ALL ($p = 0.015$) with very weak correlation ($r = -0.172$). Children with poor nutritional status pre-chemotherapy were known that most children (86,7%) experience hematological toxicity post chemotherapy. Based on this, children with ALL who have less nutritional status before undergoing chemotherapy have greater potential to experience hematological toxicity after chemotherapy. So the nutritional status in children with ALL became one of attention for health worker espesially nurse during giving nursing care to children with ALL who underwent chemotherapy. If it is known that the patient's nutritional status is not good enough, the nurse can develop a good nursing plan and provide interventions about whether the

child's nutritional obstacles such as nausea, vomiting or decreased appetite. Because most of the decline in nutritional status due to the effects of chemotherapy that causes nausea, vomiting or decreased appetite so that this affects the nutritional status of patients.

In this study, in addition to nutritional status is very thin and thin, a small proportion of ALL children who underwent chemotherapy also have nutritional status of obese (18.7%) and obesity (17.7%). Children with ALL who have obese nutritional status are known to be 54.1% have hematological tocixity but 45.9% do not experience haematological toxicity. Almost most children with ALL who have obese nutritional status do not experience hematological toxicity compared with children with ALL who have malnutrition status. According to some studies it is known that children with ALL who undergo chemotherapy with obese nutritional status that tends to appear is a metabolic disorder that is the occurrence of leukocytosis (Sari, Windiastuti, Cempako, & Devaera, 2010). In this study the occurrence of leukocytosis or thrombocytosis is not used as criteria of hematological toxicity. Because based on the Common Terminalogi Criteria for Adeverse Event (CTCAE v3) leukocytosis or thromocytosis excludes hematological toxicity, it is said to be hematological toxicity in the event of a decrease in blood cells. Although leukocytosis and thrombocytosis do not mean anything good, leukocytosis and thrombocytosis are based on studies said to be associated with the prognosis of children with ALL undergoing chemotherapy (Sari, Windiastuti, Cempako & Devaera, 2010).

In this study also known that children with normal nutritional status ALL was most (71.9%) experienced hematological toxicity. Although it is known from various studies that only extreme nutritional status (less nutrition and more nutrition) has a tendency to experience toxicity while undergoing chemotherapy (Hijiya, et al., 2006). But when see five factors that influence the occurrence of hematological toxicity (ie age, bone marrow reserve, chemotherapy type, radiation type and status nutrition) that the need for screening and analysis by researchers in this study. The age of children with ALL in this study was not seen in certain age criteria, although the investigators had conducted homogeneity tests where it was known that age in this study had the same (homogeneous) variant (p = 0,586). Bone marrow reserve in this study was also said to be better because of the selection phase of chemotherapy, which in the consolidation phase and maintenance of tumor burden has decreased and in remission. Type of chemotherapy in this study has followed the standard of chemotherapy treatment in children with ALL so that the type of chemotherapy in all respondents were the same. This type of radiation was not associated with this study because in the treatment of children with ALL radiation treatment was not performed. While the nutritional status factor is a factor that become the research material in this research.

In this study all the factors that can lead to hematological toxicity has been tried screening, but children with ALL who have good nutritional status still experience hematological toxicity. Another possibility that can lead to hematological toxicity in children with ALL undergoing chemotherapy is the association with thiopurine S-methyltransferase (TPMT) associated with a 6 -MP catabolism pathway, where it is known that patients with TPMT deficiency are at high risk for hematologic toxicities while patients with heterozygous TPMT have a moderate risk of hematologic toxicity(de Beaumais, Fakhoury, Medard, Azougagh, Zhang, et al.,2011). However, this is related to genetics so it will be difficult to be overcome or prevented and difficult to identify unless it is associated with the appearance of the Down syndrome in children with ALL, whereas in this study all were children with ALL without any other diagnosis.

In general, based on the results of the study it is known that there is a relationship between pre-chemotherapy nutrition status in the presence of hematological toxicity post-chemotherapy in children ALL (p = 0.015) with a very weak correlation (r = -0.172). In statistical results it is known that in this study has a ne-

gative direction (r = -0.172) where it is known that the higher levels of pre-chemotherapy nutritional status in children with acute lymphoblastic leukemia, the lower the possibility of hematological toxicity post-chemotherapy. This is in accordance with the researchers' assumption that children with ALL who have good nutritional status pre-chemotherapy then the possibility of post-chemotherapy toxicity experienced will be smaller. This is because a good nutritional status can increase the CD4 value and increase the immune system's defense against infectious processes and quality of life will be better than patients with poor nutritional status (Alcazar, et al., 2013; Miftahurachman & Wisaksana, 2015).

Based on the results of this study note that the assessment of nutritional status in children with ALL undergoing chemotherapy is important. This is done to minimize the occurrence of toxic effects of chemotherapy, especially hematological toxicity. So the importance of the assessment of nutritional status by nurses in order to make nursing care planning and interventions related to the fulfillment of nutritional needs in children with ALL especially those who have less nutritional status at the time of chemotherapy treatment. Owens, Hanson, McArthur and Mikhailov (2013) stated that nutrition has a relationship with short-term and long-term side effects after chemotherapy treatment in children with ALL so that with good nutritional status can increase the survival rates, but the need for rules in the provision and assessment of nutritional status in Children with ALL patients with ALL.

CONCLUSION

Based on the results of the study it is known that most children with ALL who underwent chemotherapy in the consolidation and maintenance phase have good nutritional status. Hematological toxicity occurs in most children and it is known that there is a relationship between the nutritional status children with ALL during chemotherapy with chemotherapy with hematological toxicity after chemotherapy with very weak correlation and negative characteristic, i.e, higher levels of pre-chemotherapy nutritional status in children with acute lymphoblastic leukemia the lower the likelihood of hematological toxicity after chemotherapy.

RECOMMENDATION

Based on the results of this study it is known that the nutritional status before chemotherapy has a relationship with toxicity after chemotherapy, so the importance of assessment of nutritional status in children with ALL before undergoing chemotherapy. Assessment of this nutritional status is not only the basis for calculating the dose of chemotherapy drugs to be used, but can also be used as a baseline in the preparation of a more comprehensive nursing care plan. Comprehensive nursing care in ALL children undergoing chemotherapy is done to prevent the adverse effects of chemotherapy. Nurses should be able to immediately develop a nursing intervention plan according to a nursing diagnosis, established and collaborated with other health workers, in order to avoid severe effect of the lack of nutrition for children with ALL. In addition, observation and monitoring the signs of hematological toxicity during and after chemotherapy is also one of the role of nurses. Although we do not have the authority to perform laboratory tests after chemotherapy, we can collaborate with doctors to conduct post-chemotherapy tests to evaluate the effects of treatment.

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