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Relationship between Chemotherapy Side Effects on Gastrointestinal System and Quality of Life of Pediatric Acute Lymphoblastic Leukemia Patients

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Abstract:- Patients with acute lymphoblastic leukemia (ALL) undergoes chemotherapy treatment. The side effects of chemotherapy correlated to gastrointestinal system were reported in 40% in-patients going through standard risk chemotherapy and all (100%) in-patients receiving high-risk chemotherapy. Some of the side effects of chemotherapy on the gastrointestinal system in ALL patients include decreased appetite, cachexia, fatigue, perianal dermatosis, even hemorrhoid due to constipation, as well as prolonged mucositis. These conditions physically and psychologically interfere with children activity and negatively impact the quality of life. This research studied the relationship between the side effects of chemotherapy specifically on the gastrointestinal system and the QOL of pediatric ALL patients so that appropriate follow-up procedures to improve QOL during chemotherapy can be planned. This was a cross-sectional study carried out at the Hematology-Oncology division Haji Adam Malik hospital. The research subjects were pediatric ALL patients aged between 2 and 18 years old, meeting the inclusion and exclusion criteria. Sampling technique was consecutive sampling. The relationships between the dependent variable (QOL) and independent variables (chemotherapy protocol and duration and side effects) were assessed by Chi-square, Mann-Whitney, and Fischer's exact tests. Multivariate analysis was used to determine the most dominant independent variable affecting the QOL of pediatric ALL patients undergoing chemotherapy. No significant relationship between chemotherapy protocol and QOL (p=0.435). No significant relationship between the duration of chemotherapy and QOL (p>0.05). There were significant relationships between chemotherapy-induced gastrointestinal disorder symptoms and QOL, such as oral mucositis (p=0.001), nausea (p=0.037), vomiting (p=0.001), and diarrhea (p=0.006). From the multivariate analysis, three independent variables that could predict the QOL of pediatric ALL patients were oral mucositis (p=0.002), nausea (p=0.040), and vomiting (p=0.019). Chemotherapy procedures for ALL treatment on pediatric patients showed a poor QOL.

Keywords:- *chemotherapy, quality of life, gastrointestinal system, acute lymphoblastic leukemia, pediatric*.

I. INTRODUCTION

Chemotherapy is one of the options for cancer treatment, which kills cancer cells to achieve a remission using anticancer substance or drugs known as cytostatic that inhibits the growth of the malignant cells [1]. There are two options of chemotherapy protocol for pediatric acute lymphoblastic leukemia (ALL) patients, such as standard risk and high risk, which are consisted of induction, consolidation intensification, and maintenance phases [2].

Cytostatic suppresses anti-apoptotic molecules and promotes apoptosis, which can affect the balance of cells during cell healing and recovery.[11] Thus, in addition to its therapeutic effects, chemotherapy can cause various side effects that affect various organs, including the gastrointestinal system [1,2].

The side effects of chemotherapy correlated to gastrointestinal system were reported in 40% in-patients going through standard risk chemotherapy and all (100%) in-patients receiving high-risk chemotherapy [3]. Exposure to chemotherapy increases the susceptibility of intestinal cells damage, especially the epithelial cells on the mucous layers, in which enterocytes are the targeted cells. Enterocytes are responsible for nutrition absorption, excretion of harmful chemicals and pathogens through muscle contraction, cellular mechanism, endocrines, immunology, and enhance intestinal permeability. Chemotherapy-induced intestinal damage includes crypt apoptosis, and villous atrophy [4]. During translocation process, the acting drugs, such as doxorubicin and cyclophosphamide, may shorten the intestinal villi and damage the mucous barrier, allowing commensal bacteria to enter the gastrointestinal system and lymphoid organs [5].

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Some of the side effects of chemotherapy on the gastrointestinal system in ALL patients include decreased appetite, cachexia, fatigue, perianal dermatosis, even hemorrhoid due to constipation, as well as prolonged mucositis. These conditions physically and psychologically interfere with children activity and negatively impact the quality of life [3]. From the psychosocial aspect, the effect of chemotherapy can be tough for the patients and their family. There is evidence on the challenges of social interaction in ALL patients and their family during the disease diagnosis and treatment [3,6].

Reduction in the quality of life (QOL), especially on the cognitive function, is reported in pediatric ALL patients undergoing induction chemotherapy. QOL refers to the social, emotional, and physical relationships during the chemotherapy treatment [7]. Assessing how the QOL is affected due to the side effects of chemotherapy is important to enable resolution to problems that might arise during the treatment process. There has been many studies assessing the relationship between QOL and chemotherapy side effects. However, most of them were only focusing on one or only a few symptoms [7]. We would like to study the relationship between the side effects of chemotherapy specifically on the gastrointestinal system and the QOL of pediatric ALL patients so that appropriate follow-up procedures to improve QOL during chemotherapy can be planned.

II. RESEARCH METHOD

This was a cross-sectional study assessing the relationship between the side effects of chemotherapy on the gastrointestinal system and the QOL of pediatric ALL patients. The study was carried out at the Hematology-Oncology division Haji Adam Malik hospital (RSUP HAM) polyclinic from October to November 2021. The research subjects were pediatric ALL patients aged between 2 and 18 years old. Children with intellectual disability, chronic digestive disorders like chronic gastritis, neurological-related diseases like hydrocephalus and CNS leukemia, and brain hemorrhage were excluded from the study. Moreover, children who were undergoing chemotherapy for other cancer types except ALL and consuming routine or long-term medication other than ALL drugs were also excluded from this study. Sampling technique used for all the research subjects was consecutive sampling.

The number of samples was calculated using the formula for hypothesis test for a single population using a correlation analysis design as follow (equation (1)) [8]:

$$n = (N/1+Ne^2)^2 \quad (1)$$

where:

n = Sample size
N = Population size
e = Acceptable percentage of error due to sampling error

thus,

$$n = (75/1+75\ 0.05^2)^2 \quad (1)$$

Giving the minimum number of samples needed in this study was 64 subjects.

Nutritional status was assessed based on the body mass index (BMI) classification, using body weight and height measurement data. Primary data, such as age, gender, parents' education and income, were obtained from interviews and questionnaires. Chemotherapy protocol of each patient was observed and categorized based on the risk; either standard risk or high risk, and the duration of chemotherapy, either under one year or over one year. Gastrointestinal disorder symptoms induced by chemotherapy were being questioned to the parents or guardians, using a yes-no question, followed by a thorough anamnesis for the ALL chemotherapy-induced gastrointestinal disorder. Quality of life (QOL) was assessed by using PedsQL 3.0 questionnaire filled by the respective parents or guardians, where score below 70% showed poor QOL and score above 70% showed good QOL.

A. Ethical Consideration

Consent for research participation was obtained from all the parents or guardians of the research subjects after prior explanation of the procedures in the research. This study has received the approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara (No: 122/KEP/USU/2021).

B. Data Analysis

Data collected were processed and analyzed using SPSS v23.0. Univariate analysis was used to describe the incidence rate of chemotherapy side effects, chemotherapy procedures that could cause gastrointestinal side effects, and duration of chemotherapy. Categorical data were presented as frequency. Numerical data were shown as mean ± SD under a normal distribution or median when data were not normally distributed. Bivariate analysis using Chi-square, Mann-Whitney, and Fischer's exact tests were used to assess the relationship between independent (QOL) and dependent (chemotherapy protocol type and duration and chemotherapy-induced gastrointestinal side effects) variables. Significance and confidence interval were at $p<0.05$ and 95%, respectively [9]. Multivariate analysis was used to determine the most dominant independent variable affecting the QOL of pediatric ALL patients undergoing chemotherapy. Multiple logistic regression was chosen for the multivariate analysis as the dependent variables were categorical data. Significance and confidence interval were at $p<0.05$ and 95%, respectively [9].

III. RESULTS

A. Research Subjects Characteristis

In this study, over half (33 people, 51.6%) of the participants were male. The youngest and eldest subjects were 2 years old and 17 years old, respectively. The majority (81.2%) of the research subjects had good nutritional status, 7 (10.%) subjects had poor nutritional status, 4 (6.3%) subjects were obese, and 1 (1.6%) subject was over-nourished. The mean age of parents was 36.55 years old, with the youngest age being 29 years old and oldest age being 52 years. The majority of patients' parents were high school graduates, in

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which 40 (62.5%) fathers and 46 (71.9%) mothers were high school graduates. There were only 10 (15.8%) fathers and 8 (12.5%) mothers who completed higher education. Over one third (24 parents, 37.5%) of parents were entrepreneurs, while the other one third (21 parents, 32.8%) were employees in privately owned companies. The remaining parents were civil servants, farmers, or police. Around one third (22 subjects, 34.4%) of the subjects come from households with below 5 million rupiah monthly income. The remaining subjects were from households with above 5 million rupiah monthly income.

Based on the chemotherapy procedures, most subjects, 40 (62.5%) patients went through standard risk protocol and 24 (37.5%) patients had high risk protocol. There were 21 (32.8%) subjects each in the induction and maintenance phase. Whereas, there were 15 (23.4)%) subjects in the consolidation phase and 7 (10.9%) subjects were in intensification phase. The mean chemotherapy duration was 23.03 weeks, with the shortest and longest duration being 1 and 88 weeks, respectively. The study showed that 36 pediatric ALL patients (56.2%) had poor QOL.

The frequency of gastrointestinal side effects on pediatric ALL patients' undergoing chemotherapy was shown in table 2, with nausea as the most reported symptoms (57 subjects, 89.1%), followed by vomiting, oral mucositis, constipation, and diarrhea with 29 (45.3%), 26 (40.6%), 25 (39.1%), and 12 (18.8%) subjects, respectively.

Subject characteristics	n = 64
Gender, n (%)	
Male	33 (51.6)
Female	31 (48.4)
Age, years	
Mean (SD)	9.44 (3.96)
Median (min – max)	10 (2 – 17)
2 – 4	6 (9.4)
5 – 7	20 (31.3)
8 – 12	23 (35.9)
13 – 18	15 (23.4)
Parents age, years	
Mean (SD)	36.55 (5.94)
Median (min – max)	34.5 (29 – 52)
Nutritional status, n (%)	
Poor	7 (10.9)
Good	52 (81.3)
Overweight	1 (1.6)
Obese	4 (6.3)
Education level (father), n (%)	
Junior high school	7 (10.9)
Senior high school	40 (62.5)
Diploma I	1 (1.6)
Diploma III	6 (9.4)
Graduate	10 (15.6)
Education level (mother), n (%)	
Junior high school	7 (10.9)
Senior high school	46 (71.9)
Diploma III	3 (4.7)
Graduate	8 (12.5)
Occupation, n (%)	
Private employee	21 (32.8)
Farmer	10 (15.6)
Civil servant	8 (12.5)
Soldiers	1 (1.6)
Entrepreneur	24 (37.5)
Parents income, n (%)	
< 5 million rupiah	22 (34.4)
5 – 9 million rupiah	40 (62.5)
≥ 10 million rupiah	2 (3.1)
Mean (SD), million	5.02
Median (Min – Max), million	5 (3 – 15)
Chemotherapy procedures, n (%)	
Standard Risk	40 (62.5)
High Risk	24 (37.5)
Chemotherapy phase, n (%)	
Induction	21 (32.8)
Consolidation	15 (23.4)
Maintenance	21 (32.8)
Intensification	7 (10.9)
Symptoms and complaints	
Oral mucositis, n (%)	26 (40.6)
Nausea, n (%)	57 (89.1)
Vomiting, n (%)	29 (45.3)
Diarrhea, n (%)	12 (18.8)
Constipation, n (%)	25 (39.1)

Table 1: Research subjects characteristic

B. Relationship between Chemotherapy Procotocol on Gastrointestinal Side Effects on QOL

There were 21 out of 40 subjects (52.5%) who underwent high risk chemotherapy had poor QOL. Also, 15 out of 24 subjects (62.5%) who underwent standard risk chemotherapy had poor QOL. Data analysis using chi-square test on the relationship between different chemotherapy protocol on gastrointestinal side effects and QOL in pediatric ALL patients showed no significant relationship between the standard or high risk protocol and QOL, with p=0.435.

Subject characteristics	QOL		p	RP 95%CI
	Poor	*Good*		
Chemotherapy procedures, n (%)				
High risk	21 (52.5)	19 (47.5)	0.435[a]	0.840
Standard risk	15 (62.5)	9 (37.5)		0.548-1.288

Table 2: Relationshop between chemotherapy protocol and the quality of life

[a]Chi-square test

C. Relationship between Duration of Chemotherapy on Gastrointestinal Side Effects and QOL

The research subjects underwent chemotherapy for at least 1 week to up to 88 weeks. In the group with poor QOL, the mean chemotherapy duration was 21.11 weeks, with a median value of 11 weeks. In the group with good QOL, the mean chemotherapy duration was 25.5 weeks, with a median value of 17 weeks. This study showed no significant

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relationship between the duration of chemotherapy and QOL, with p>0.05 using Mann-Whitney test.

Subject characteristics	QOL		p	RP 95%CI
	Poor	*Good*		
Duration of chemotherapy, weeks				
Mean (SD)	21.1(24.6)	25.5 (23.48)	0.353[b]	-
Median (Min – Max)	11 (1-88)	17 (1-87)		

Table 3: relationship between the duration of chemotherapy and the quality of life

[b]Mann-Whitney test

D. Relationship between Side Effectts of Chemotherapy on Gastrointestinal System and QOL

Table 4 showed the relationship between the side effects of chemotherapy on gastrointestinal system and QOL of pediatric ALL patients. There was a significance between oral mucositis and patients' QOL, p=0.001, where 21 (80.8%) out of 26 patients with oral mucositis had poor QOL. In comparison, 23 (60.5%) out of 38 patients without oral mucositis had good QOL.

This study also showed a significance between nausea and QOL (p=0.037). Fischer's exact test showed that 35 (61.4%) out of 57 patients with nausea symptoms had poor QOL, while only one (14.3%) out of 7 patient without nausea had poor QOL.

A significance was also observed between vomiting and QOL (p=0.001). Chi-square test showed that 23 (80.8%) out of 29 patients with vomiting symptoms had poor QOL, while 22 (62.9%) out of 35 patients without vomiting had good QOL.

Furthermore, a significance was seen between diarrhea and QOL (p=0.006). Chi-square test showed that 11 (91.7%) out of 12 patients with diarrhea symptoms had poor QOL, while over half, 27 (51.9%) out of 52 patients without diarrhea symptoms had good QOL.

On the other hand, no significance was observed between constipation and QOL on the pediatric ALL patients who underwent chemotherapy (p=0.287). Chi-square test showed that 12 (48%) out of 25 patients with constipation had poor QOL, while 24 (61.5%) out of 39 patients without constipation had poor QOL.

Subject characteristics	QOL		p	RP 95%CI
	Poor	*Good*		
Side effects, n (%)				
Oral mucositis				
Yes	21 (80.8)	5 (19.2)	0.001[a]	2.046
No	15 (39.5)	23 (60.5)		1.323-3.165
Nausea				
Yes	35 (61.4)	22 (38.6)	0.037[c]	4.298
No	1 (14.3)	6 (85.7)		0.692-26.693
Vomiting				
Yes	23 (79.3)	6 (20.7)	0.001[a]	2.135
No	13 (37.1)	22 (62.9)		1.335-3.414
Diarrhea				
Yes	11 (91.7)	1 (8.3)	0.006[a]	1.907
No	25 (48.1)	27 (51.9)		1.371-2.652
Constipated				
Yes	12 (48)	13 (52)	0.287[a]	0.780
No	24 (61.5)	15 (38.5)		0.484-1.257

Table 4: Relationship between gastrointestinal side effects on the quality of life

[a]Chi-square test, [c]Fisher's Exact test

E. Multivariate Analysis for Chemotherapy Side Effectts on Gastrointestinal System and QOL

The independent variables that were taken for multivariate analysis were those with p<0.25 from bivariate analysis, which were oral mucositis (p=0.001), nausea (p=0.037), vomiting (p=0.001), and diarrhea (p=0.006).

Using the enter method in the multivariate analysis (table 5), there was a total of three selection processes, where a few independent variables in the first and second selection processes were with p>0.05. From the final model of the multivariate analysis, three independent variables that could predict the QOL of pediatric ALL patients were obtained, which were oral mucositis (p=0.002), nausea (p=0.040), and vomiting (p=0.019).

Exp(B) value showed that nausea was the most dominant factor of the independent variables that could affect the QOL of pediatric ALL patients with value of 16.033 (95% CI 1.141 – 225.362). This means that pediatric ALL patients with nausea symptom had 16.033 times increased risk of having poor QOL compared to those without the symptom.

The second most dominant independent variable that could affect the QOL of pediatric ALL patients was oral mucositis. Children with oral mucositis had 13.317 times increased risk of getting poor QOL (95%CI 2.557 – 69.360) compared to those without. Furthermore, multivariate analysis on the vomiting symptom showed that patients with the symptom had 4.815 times increased risk of getting poor QOL (95% CI 1.288 – 17.995) than those without.

The probability of QOL of pediatric ALL patients could be predicted through regression equation. There was a probability of 95.9% for a pediatric ALL patient to have oral mucositis, nausea, and vomiting as side effects from chemotherapy.

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Variables	B	p	Exp(B)	95% CI for Exp (B)	
				Lower	*Upper*
Oral Mucositis	2.589	0.002	13.317	2.557	69.360
Nausea	2.775	0.040	16.033	1.141	225.362
Vomiting	1.572	0.019	4.815	1.288	17.995

Table 5: multivariate analysis on the relationship between gastorintestinal side effects from chemotherarpy and the quality of life

IV. DISCUSSION

In this study, most patients (51.6%) were male. A study done at Hasan Sadikin hospital by Angkasa, Suryawan, and Prihatni also showed similar findings where higher proportion (59.9%) of pediatric ALL patients were male [10]. The explanation on higher incidence rate of ALL in male are not fully known although the current Genome-wide Association Study (GWAS) showed that genetics plays a role on the issue [11].

The proportion of patients with good nutritional status in this study was 81.2%. A study by Herintya, Mulatsih, and Prawirohartanto showed a good nutritional status in 56% of the total sample of pediatric ALL patients with 80% remission. However, their study did not show the relationship between nutritional status and recurrence, but instead, with death rate [12]. Permatasari, Windiastuti, and Satari assessed the life expectancy and prognostic factors on pediatric ALL patients and found no significance on survival rate between gender and nutritional status. It suggested that nutritional status did not affect the QOL of pediatric ALL patients [13].

Most participants (62.5%) had standard risk chemotherapy procedures. The classification was assigned through Berlin-Frankfurt-Mu¨nster (BFM) trial by considering the clinical and laboratory criteria evaluated from previous procedures, which was classified to standard and high risk. This did not agree with the study by Trujillo, Linares, and Sarmiento where only 10.8% of patients undergoing standard risk chemotherapy with no death reported [14]. Patients with standard risk therapy had a higher life expectancy than those undergoing intermediate and high-risk therapy, where the probability of event-free survival (pEFS) in 6 months was reported as 89.5% [15]. The type of chemotherapy procedures given at various places could be different depending on the ALL patients' characteristics.

Induction and maintenance phase were the most reported phases in this study, contributing to 32.8% of the cases. Chemotherapy was given in four phases: remission induction, consolidation, reinduction, and maintenance. The treatment response on each phase would have different clinical outcomes [16]. Abdelmabod et al studied the clinical outcomes from ALL treatment in children and found that 23% patients died during induction phase, which mostly related to infection [17].

The longest and shortest duration of chemotherapy was 88 weeks and one week, respectively, with mean duration of 23.03 weeks. This was relevant to the study comparing the survival rate of pediatric patients with ALL with 2013 and 2006 protocols, which found out the duration of ALL chemotherapy varied between 1.5-3 years, to eradicate the cancer cells population [18].

In this study, 56.2% of pediatric ALL patients had poor QOL. The QOL assessment on pediatric ALL patients are important so that patient and parents could anticipate incidents that could occur during the therapy. QOL assessment could also help parents and medical staffs to strategize for QOL improvement of the patients. In addition to QOL, identifying the determinant for QOL is also critical. A study in Bali done in 2020 showed that parents with high income, undergoing standard risk chemotherapy, and male were the determinant factors for higher QOL in pediatric ALL patients after the induction phase [19]. This suggested that QOL of the patients were influenced by many factors.

The most reported gastrointestinal side effect from the pediatric ALL patients in this study was nausea (89.1%) while diarrhea (18.8%) was the least common. This agreed with Fatikasari, Ayu, and Masruhim who did a study on chemotherapy in pediatric leukemia patients at Abdul Wahab Sjahranie hospital in Samarinda. It was found that nausea-vomiting, 97%, was the most common side effect and ondansetron was prescribed to reduce the symptoms [20].

In this study, the chemotherapy procedures were grouped into standard and high risk. There was no significance between chemotherapy procedures and QOL as both patients undergoing standard and high-risk procedures had poor QOL. Criteria for pediatric ALL patients treated with high-risk procedures include <1 or >10 years when diagnosed, leucocytes >50000x10^9/L, >15/3 leukemia cells in cerebrospinal fluid, mediastinal mass >2/3 from the diameter of thoracic cavity, had bilineage and T-cell leukemia. Pediatric ALL patients were treated with standard-risk procedure when no signs from high-risk procedures were observed [18]. The results in this study were not in line with Yulianti and Adnan who analyzed the prognostic factors on 5 years survival of ALL patients in children aged 1-18. It showed that high risk group had 7.69 increased risk of death compared to standard risk group [21].

Another study comparing standard and high-risk procedures by Permatasari, Windiastuti, and Satari found that patients who did standard risk procedures had a higher death risk within five years compared to high risk [13]. The difference might be due to the larger population of standard risk patients in this study compared to the high risk where patients with standard risk had a better QOL, thus, no difference was observed between different chemotherapy procedures and poor QOL.

A study at Sardjito hospital in 2017 found that patients with high-risk procedures had a 2.06 increased death risk compared to patients with standard risk [22]. Jaime-Perez et al studied the clinical outcomes on pediatric ALL patients undergoing standard and high-risk procedures through

overall survival (OS) and event-free survival (EFS). The OS within 5 years on high-risk group was 51±5.51%, with median of 60.91 months, compared to standard risk group, 80.9±4.35% (p<0,001). Both OS and EFS median were not achieved on the standard risk group. Based on the risk group, 59 (78.7%) and 16 (21.3%) deaths were observed in high and standard risk group, respectively (p<0.001) [23].

There was no significance between the duration of chemotherapy on the gastrointestinal side effects and QOL of pediatric ALL patients. A similar findings was also seen in a study by Yakin, Syarif, and Tehuteru Despite the difference in chemotherapy duration, the remission in 2006 and 2013 protocols had almost similar values, 32% and 29% [18]. Polanska et al showed a similar findings to our study where the duration of chemotherapy was not significant to the clinical outcomes of ALL patients (p=0.636) with weak correlation (r=0.056). However, the duration of chemotherapy affected the cognitive function of the pediatric patients (p=0.046) [24].

Teachy et al in Philadelphia did a study related to therapy optimalization in modern era, and the difference in the duration of maintenance ALL therapy. This was a metanalysis study involving 16 trials. Recurrence was more often seen in the shorter duration of therapy, although death due to toxicity was more common. Furthermore, patients with shorter duration of therapy were easier to be cured. Thus, there was no different in OS on the overall cohort studies or the sub analysis based on age, initial white blood cells count, or gender. However, it was stated that longer therapy duration would cause more loss although no supporting evidence was provided [25].

Chemotherapy is a long, continuous, and regular process for children with cancer. The side effects during treatment could cause physical inconveniences such as nausea, vomiting, oral mucositis, hair loss, and nerve damage such as numb and tingling in fingers and toes. In addition to the physical problems, children would also face psychological issues such as lacking confidence, cognitive disorder, anxiety, and depression. Parents were asked to understand the disorders experienced by the children and to give supports during treatment to improve the QOL, especially on the physical health dimension [26].

The gastrointestinal side effects that were significant to the QOL of pediatric ALL patients in this study were oral mucositis, nausea, vomiting, diarrhea, and constipation. Aggressive radiation during chemotherapy could affect and worsen the general health condition and QOL of the ALL survivors. The side effects or infection related to the chemotherapy could be the cause for morbidity and mortality of ALL patients. It could be seen in literatures that 24% of the chemotherapy-related infection occurred in the oral cavity. Early intervention or prevention could significantly reduce the oral complication related to myelosuppression treatment. It is important to evaluate oral health and remove the source that could cause potential infection in patients together with the therapy. This infection could last for three weeks, starting from 3-5 days after initial chemotherapy dose and reach its peak in 7-14 days [27].

A study by Mendonca et al involving 103 pediatric ALL patients with oral mucositis showed that oral mucositis occurred in 65 patients in day 14 and 38 patients in day 56. Patients generally had ulcer in mucous layer, roof of mouth, lips, and hard palate. Lesion was followed by pain, hyperemia, and fibrin deposition. The mean time for oral mucositis to occur was 6.8±3.9 days [28].

Figliolia et al studied the oral mucositis in pediatric ALL patients and found that 46% had the mucositis during chemotherapy treatment. The multivariate regression analysis showed a significant risk of oral mucositis, and it is concluded that chemotherapy-induced oral mucositis should be analyzed prospectively and systematically in the specific treatment centers for ALL to establish the toxicity level of chemotherapy drugs and to improve patients' QOL through therapeutic approach and a more effective prophylaxis for preventive treatment [29].

A case report by Dwiarie, Nur'aeny, and Nainggolan explained that an ALL patient with oral mucositis had a low QOL score of 46 according to The Functional Assessment of Cancer Therapy-General (FACT-G) and 58 according to Oropharyngeal Mucositis Quality of Life (OMQoL). However, an increase in the FACT-G and OMQoL scores was observed after treatment to 54 and 93, respectively [30].

A study by Aroso reported oral manifestation in ALL patients both through natural occurrence and treatment. One of the most common manifestation was oral mucositis. This study concluded that dentists could contribute to the higher survival rate and improvement of QOL for ALL patients through early diagnosis, support for antineoplastic treatment, and long-term maintenance and monitoring. Thus, dentist could be an important element in the multidisciplinary team in the hematology-oncology division for ALL treatment in children [31].

Novrianda and Arif studied oral mucositis and the oral mucositis specific QOL on cancer patients undergoing chemotherapy and showed a mean score of 58.61. The diet and swallowing subscales had the lowest scores, 55.00 and 55.75, respectively. There was no significance observed in the oral mucositis specific QOL between mild and severe mucositis (p>0.05) [32].

Nausea and vomiting were some of the reported gastrointestinal side effects related to QOL of pediatric ALL patients in this study. This was not in agreement with a study by Polanska et al which showed no significance between nausea and vomiting with QOL of pediatric ALL patients (p=0.476) [24]. On the other hand, our study agreed with Dupuis et al. (2016) where nausea during chemotherapy treatment was significantly related to patients' QOL (p<0.0001) using Pediatric Quality of Life Inventory (PedsQL) [33].

A descriptive research by Pujiati assessed the physical health dimension within the QOL of children with leukemia at RSUD dr. Moewardi. The study showed children undergoing treatment at the hospital had limited activity, complaints of sores, difficulty in walking, fatigue, and unwillingness to get treated due to the fear of pain, nausea,

and vomiting after treatment session. It was reported that 56.7% patients had poor QOL due to the mentioned symptoms [26].

Diarrhea was the least reported side effects in pediatric ALL patients. This was relevant to the study by Anver, Mantik, and Manopo assessing the clinical signs of diarrhea in pediatric ALL patients undergoing chemotherapy. There were only 28% of patients with diarrhea from the entire research sample population, while 23.5% of patients had diarrhea accompanied by vomiting [34].

There have been no studies to assess the relationship between diarrhea and QOL of pediatric ALL patients due to the low incidence rate of diarrhea. However, severe chemotherapy-induced diarrhea could cause fluid loss, life threatening dehydration, electrolytes imbalance, and renal insufficiency. Nutrients deficiency due to changes in gastrointestinal transit time and digestion function could give a negative effect on QOL. Diarrhea was also linked with the increased risk of infection complication on chemotherapy-induced neutropenia [35].

Ebert and Hagspiel did a review on clinical signs of gastrointestinal system on leukemia. The use of antimycotic was linked with increased survival rate and reduced duration of diarrhea. The mortality rate of Neutropenic enterocolitis (NE), where 38% of the reported symptoms were diarrhea, had recently reduced due to a more rapid diagnosis, advancement in supportive care, and faster surgery and medical therapy provided [36].

The multivariate analysis in this study showed oral mucositis, nausea, and vomiting as the independent variables that could predict the QOL of pediatric ALL patients. Nausea was the most dominant factor affecting the QOL where pediatric ALL patients with nausea would have a 16.033 increased risk of poor QOL compared to those without the symptoms.

Nausea and vomiting were the most common side effects of chemotherapy which causes inadequate nutrition supply, electrolyte imbalance, increased anxiety level, stress, and depression. Some studies reported nausea as one of the most common symptoms in pediatric cancer patients. In addition to chemotherapy, nausea and vomiting could also cause by radiation, use of opioid, intestinal obstruction, and emotional disorders. This review assessed the health-related quality of life (HRQOL) where the HRQOL in cancer patients were related to pain and nausea [37].

The probability of a pediatric ALL patient with side effects of oral mucositis, nausea, and vomiting to have a poor QOL was 95.9%. A worse QOL on patients undergoing high risk chemotherapy was observed in all treatment phases. Specifically, pain, nausea, anxiety score, physical appearance and cognitive problems were significantly worse in patients undergoing high risk chemotherapy [19].

Medical team needs to educate patients during chemotherapy as the procedures and duration could have a risk on the QOL of pediatric ALL patients. We could predict children' QOL through the gastrointestinal side effects, which could be used as a consideration when educating patients and family.

V. CONCLUSION

Chemotherapy procedures for ALL treatment on pediatric patients showed a poor QOL. Significance was seen between oral mucositis, nausea, vomiting, and diarrhea on the QOL of ALL pediatric patients.

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