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Original Article

The Correlation between chemotherapy agents and alopecia in childhood acute lymphoblastic leukemia at Dr. Mohammad Hoesin General Hospital Palembang

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Abstract

Background Alopecia is the most common side effect of chemotherapy agents via disruption of metabolic growth and mitotic processes of hair follicles, leading to shaft damage and hair loss. Alopecia may cause psychological and social problems.

Methods A cross-sectional descriptive study was conducted in pediatric Hemato-Oncology clinic and wards of RSMH from February to March 2023. Sixty patients were selected using purposive sampling. Medical records, chemotherapy protocol, and questionnaires were obtained. Alopecia was diagnosed clinically and using visual aid.

Results Out of 60 patients, 39 were boys and 21 were girls. Subjects were predominantly 6-11 years old (46.7%), acute lymphoblastic leukemia (ALL) standard risk (55.0%), and phase maintenance I chemotherapy (48.3%). Common patterns of alopecia were frontal (18.5%) and vertex (18.1%). Methotrexate, vincristine, daunorubicin, and L-asparaginase represented majority of combination chemotherapy that resulted in alopecia (63.3%) at 3-6 weeks of treatment (48.3%). Most hair loss was found on pillow (65.9%).

Conclusion Age, risk stratification, chemotherapy phase, and alopecia onset significantly correlated with chemotherapy agents.

Key words
Alopecia; Acute lymphoblastic leukemia; Chemotherapeutic agents; Childhood.

Introduction

Acute lymphoblastic leukemia (ALL) is a hematology malignancy of the bone marrow characterized by proliferation of immature lymphoid cells in the peripheral circulation. In Indonesia, the incidence of ALL reaches 2.5-4.0 per 100,000 children, with 2,000-3,000 cases anually, with the highest incidence in 1-4 years old.[1] Prevalence of ALL at Dr. Mohammad Hoesin Hospital (RSMH) Palembang 2011-2018 was 261 patients.[2]

Chemotherapy is one of treatment modalities for cancer. Chemotherapy agents in ALL can be divided as standard risk (SR) and high risk (HR). Methotrexate (MTX), vincristine (VCR), 6-mercaptopurine (6-MP), daunorubicin, L-asparginase (L-asp), cyclophosphamide, and cytarabine are mostly used in children with ALL. Alopecia is the most common (65%) side

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effect of chemotherapy.[3,4]

Chemotherapy interfere mitotic and metabolic processes of hair follicle growth, thus hair shafts become thinner and easily break with minor trauma.[5] Chemotherapy-induced hair abnormalities are generally reversible. It also has psychological impact on both children and parents, including anxiety, depression, and inconfidence that affect social life.[3,6,7] However, there are limited studies about alopecia in Indonesia. There has been no data on hair disorders due to chemotherapy agents in RSMH Palembang. The purpose of this study is to assess the correlation between chemotherapy agents and alopecia in childhood ALL at RSMH Palembang.

Methods

This is a cross-sectional descriptive study using data from medical record of childhood ALL patients within 2021-2022 in pediatric Hemato-Oncology clinic and wards of RSMH Palembang. Purposive sampling was used, including all who meet inclusion and exclusion criteria. Inclusion criteria are patients 1-18 years old diagnosed with ALL who received chemotherapy. Patients with history of hair disorders (e.g. alopecia areata) before receiving chemotherapy, lupus, scalp and hair infections, on therapy for hair disorders, and relapsed ALL were excluded. Written consent were all retrieved from parents after explanation.

Gender, age, and ALL type data were obtained from medical records. Chemotherapy phase and agents causing alopecia; onset, pattern, and impact on psychosocial well-being were ALL obtained from chemotherapy protocols and questionnaires. Questionnaires were completed by parents. We evaluated the distribution of alopecia during chemotherapy in frontal, vertex, temporal, occipital, and parietal regions using the alopecia visual aid (*Olsen EA, Canfield DC. Canfield Scientific; Fairfield, NJ*). The data was collected, categorized, analysed, and presented in tables and narratives. Data analysis was using SPSS *(Statistical Package for the Social Sciences)* version 22.0 (In Corporation, Chicago, Illnois, 2015). Descriptive variables were analyzed with frequency and Chi-square test. P value of <0.05 was considered significant. This study was approved by the ethics committee of health research and development (No.LB.02.03/XVII.5.11/ETIK/28/2024).

Results

There were total 60 patients of pediatric ALL at RSMH Palembang from February to March 2023 who met the inclusion criteria. The number of patients with pediatric ALL were 60 cases (22.5%) and 207 cases (77.5 %) in 2021 and 2022, respectively. Demographic and clinical profile were shown in **Table 1**.

There were 39 (65%) boys and 21 (35%) girls. The majority were 6-11 years old. There were 27 patients (45%) with HR, 33 patients (55.0%) with SR, 29 patients (48.3%) were in maintenance I, and 14 patients (23.3%) in maintenance II. Alopecia mostly found in induction (68.3%) and consolidation (28.3%) phase. Patterns of alopecia were found in frontal (18.5%), and vertex and parietal (18.1%) region. Chemotherapy-induced alopecia was found in 38 patients (63.3%) with combination of MTX, VCR, daunorubicin, and L-asp. The onset of alopecia was 3-6 weeks after first chemotherapy in 48.3% of patients. Hair loss was mostly found on pillows (65.9%).

Pearson Chi square test showed no significant correlation between gender and chemotherapy agents (p=0.246). In contrast, age, ALL risk stratification, and alopecia onset had significant correlation with chemotherapy agents. Alopecia

Tabel 1 Demographic and clinical profile data.

Characteristics/Category	*n (%)*
Gender	
Boys	39 (65)
Girls	21 (35)
Age group (year)	
1-5	22 (36.7)
6-11	28 (46.7)
12-18	10 (16.7)
Stratification of ALL risk groups	
SR	33 (55.0)
HR	27 (45.0)
Pattern of alopecia	
Vertex	50 (18.1)
Frontal	51 (18.5)
Parietal	50 (18.1)
Temporal dextra	49 (17.8)
Temporal sinistra	47 (17.0)
Chemotherapy phase	
Occipital	29 (10.5)
Induction	2 (3.3)
Consolidation	11 (18.3)
Intensification	2 (3.3)
Maintenance 1	29 (48.3)
Maintenance II	14 (23.3)
Completed	2 (3.3)
Chemotherapy agents	
MTX, VCR, daunorubicin, L-asp	38 (63.3)
Mt It, MTX, CP, 6-MP	4 (6.7)
MTX, VCR, daunorubicin	1 (1.7)
Mt It, MTX, 6-MP	10 (16.7)
VCR, L-asp, MTX	1 (1.7)
Mt It, VCR, daunorubicin, L-asp	1 (1.7)
Mt It, MTX, VCR, CP, 6-MP	1 (1.7)
MTX, VCR, 6-MP	2 (3.3)
Mt It, daunorubicin,MTX,CP,6-MP	2 (3.3)
Onset of alopecia	
5 days – 2 weeks	14 (23.3)
3 – 6 weeks	29 (48.3)
7 weeks – 2 months	17 (28.3)
Hair loss findings	
Pillow	56 (65.9)
Comb	10 (11.8)
Clothing	13 (15.3)
Towel	6 (7.1)

SR: standard risk, HR: high risk, MTX: methotrexate, Mt It: intrathecal methotrexate, VCR: vincristine, L-asp: L-asparginase, 6-MP: 6-mercaptopurine, CP: cyclophosphamide.

was more common in induction phase with the use of combined MTX, VCR, daunorubicin, and L-asp (p=0.000) **(Table 2)**.

According to the questionnaire filled by parents, only 25% of them had received consultation about chemotherapy-induced hair loss. In addition, 39.9% believe and accept that hair loss was part of therapy, 19.1% said that hair loss was the worst side effect. About 14.5% stated that hair loss affects their children's social life. As for self-adjustment, 34.7% used wigs/ accessories, 19.0% shaved/cut their children's hair, and 41.3% were not doing any self-adjustment.

Discussion

Acute lymphoblastic leukemia (ALL) is one of the most common hematological malignancies in children, with increasing incidence every year. Similarly, the number of ALL are also increased in RSMH, in line with Elisafitri R *et al;* as they showed an increased of ALL prevalence from 60 cases in 2015 into 67 cases in 2017, mostly in children.[8] This finding is likely due to increased number of cancer centers, increased public awareness, better infrastructure, referral systems and training program that improves diagnosis, reporting, and access to clinical care.[9]

This study found that the ratio of boys and girls with ALL was 1.8:1. Similarly, Kakaje *et al.* found that ALL is 1.5 times more common in boys.[10] Yulianti *et al.* also found male predominance with 62.31%.[11] The explanation of this gender difference is still not understood.[12]

ALL commonly affects children under 15 years old with prevalence of 25%. Kakaje *et al.* also found that the highest age group of childhood ALL was 5-9 years (48.8%).[10] The most common age group in this study was 6-11 years (46.7%), similar with Sitaresmi *et al.* where the average age of childhood ALL was 6 years old.[13] Some of the risk factors associated with ALL include genetics, disorders of immune system, maternal lifestyle during pregnancy, radiation and chemical exposure.[14] This study found that SR ALL was higher than HR. In line with

Tabel 2 Correlation between variables and chemotherapy agents in patients with childhood ALL.

Characteristics	*Chemotherapy agents*									*P value*
	MTX, VCR, daunorubicin, L-asp	*Mt It, MTX, CP, 6-MP*	*MTX, VCR, daunorubicin*	*Mt It, MTX, 6-MP*	*VCR, L-asp, MTX*	*Mt It, VCR, daunorubicin, L-asp*	*Mt It, MTX, VCR, CP, 6-MP*	*MTX, VCR, 6-MP*	*Mt It, daunorubicin, MTX, CP, 6-MP*	
Gender										
Boys	26 (43.3)	2 (3.3)	0 (0.0)	8 (13.3)	1 (1.7)	1(1.7)	0 (0.0)	0 (0.0)	1 (1.7)	0.246
Girls	12 (20.0)	2 (3.3)	1 (1.7)	2 (3.3)	0 (0.0)	0 (0.0)	1 (1.7)	2 (3.3)	1 (1.7)	
Age (years)										
1-5	13 (21.7)	1 (1.7)	0 (0.0)	6 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.7)	
6-11	21 (35.0)	0 (0.0)	1 (1.7)	4 (6.7)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0.018*
12-18	4 (6.7)	3 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	1(1.7)	1(1.7)	0 (0.0)	1 (1.7)	
Stratification of ALL risk groups										
SR	20 (33.3)	0 (0.0)	1 (1.7)	10 (16.7)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0.012*
HR	18 (30.0)	4 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.7)	1 (1.7)	2 (3.3)	
Alopecia pattern										
Vertex	6 (10.0)	0 (0.0)	1 (1.7)	4 (6.7)	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.7)	1 (1.7)	
Frontal	8 (13.3)	2 (3.3)	0 (0.0)	2 (3.3)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Parietal	6 (10.0)	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0.405
Temporal dextra	9 (15.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Temporal sinistra	7 (11.7)	1 (1.7)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	
Occipital	2 (3.3)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	
Chemotherapy phase										
Induction	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Consolidation	6 (10.0)	1 (1.7)	1 (1.7)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.7)	
Intensification	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.153
Maintenance I	19 (31.7)	2 (3.3)	0 (0.0)	4 (6.7)	1 (1.7)	0 (0.0)	0 (0.0)	2 (3.3)	1 (1.7)	
Maintenance II	8 (13.3)	1 (1.7)	0 (0.0)	5 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Completed	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Alopecia during chemotherapy phase										
Induction	38 (63.3)	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.7)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	
Consolidation	0 (0.0)	4 (6.7)	0 (0.0)	10 (16.7)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	2 (3.3)	0.000*
Maintenance I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0,0)	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	
Alopesia onset										
5 days – 2 weeks	11 (18.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.7)	1 (1.7)	0 (0.0)	0 (0.0)	
3 – 6 weeks	26 (43.3)	0 (0.0)	1 (1.7)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0.000*
7 weeks – 2 months	1 (1.7)	4 (6.7)	0 (0.0)	9 (15.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	2 (3.3)	

*Pearson Chi-Square test, p=0.05

Sitaresmi *et al;* where SR was found in 29.57%.[13]

In accordance with Olsen's pattern, males alopecia occurs in frontal, temporal, middle, and vertex; while in females, it begins in frontal region and vertex in the later stages **(Figure 1)**. According to Spanish consensus, occipital, frontal, and total alopecia were more common in males in decreasing order, in comparison to total, frontal, and occipital alopecia in females.[15] Alopecia often affects frontal and occipital as they are more sensitive. Hairs in anagen phase undergo apoptosis post chemotherapy. In contrast, hairs in telogen phase not affected by chemotherapy. Hairs in the scalp hairline area are resistant to chemotherapy, thus the prognosis was poor when alopecia occurs in hairline area. Chemotherapy agents enhance the activity of androgen hormones, thus features of alopecia resembe androgenetic or female-pattern alopecia. Alopecia occur in vertex and temporal areas caused by mechanical friction with sheets, pillows, combs, and head covers.[16] This study showed that 65.9% of hair loss was found on pillows. The pattern of alopecia in children was difficult to identify because they had shaved their hair before chemotherapy.[5]

In this study, 29 patients (48.3%) had alopecia in 3-6 weeks after initiation of chemotherapy, similar with other studies.[5,17,18] In contrast, Vagace *et al.* found that hair loss started 7-10 days after therapy initiation and became more pronounced within 1-2 months of therapy.[19] Chemotherapy agents disrupt mitotic and metabolic processes in actively growing hair, causing hair shaft become thin and vulnerable to trauma. Hair follicles will then undergo apoptosis-induced regression (catagen) followed by telogen.[5,20]

Chemotherapy agents that often causes alopecia are alkylating agents, antimetabolites, vinca alkaloids, and topoisomerase inhibitors.[5]

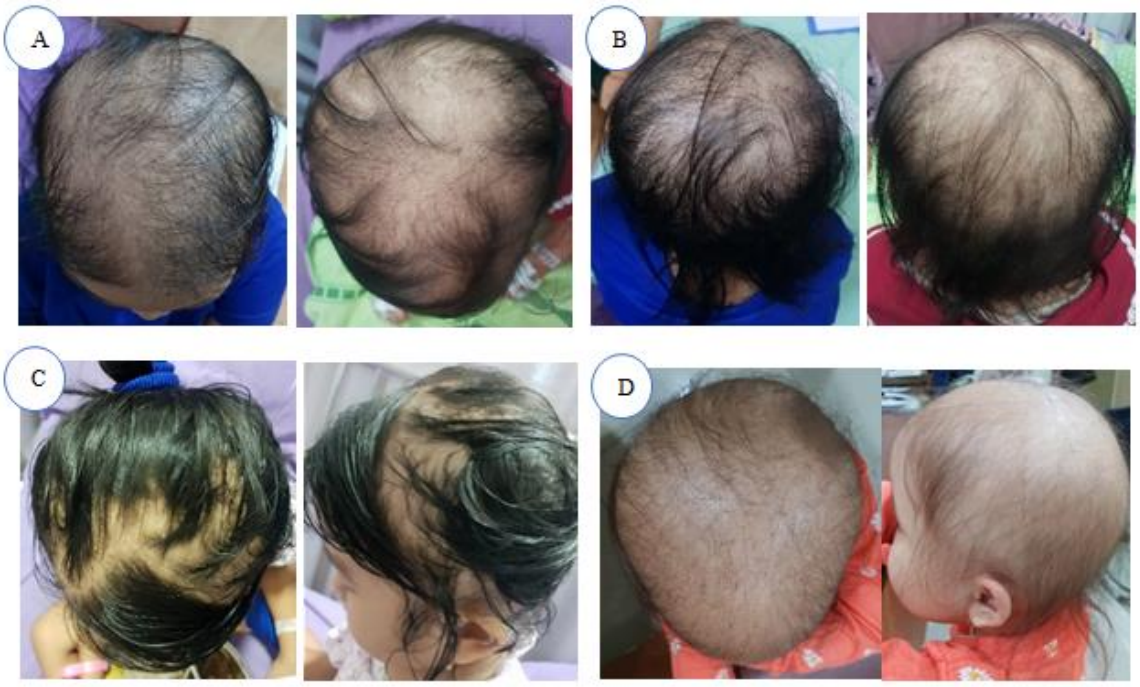

Figure 1 Alopecia pattern in patients with childhood ALL receiving chemotherapy, (A) frontal, (B) vertex, (C) frontal, (D) frontal, vertex, parietal, and temporal. (Photo documentation of pediatric ALL patient at RSMH Palembang).

This study found that induction phase of combination of MTX, VCR, daunorubicin, and L-asp 38 (63.3%) leads to alopecia. Saraswat *et al.* found that chemotherapy agents lead to cutaneous side effects and reduce the quality of life.[3] Some showed hair loss is move severe in combination of more agents. Pavey *et al.* showed that combinations of several agents cause anagen effluvium.[18] Chemotherapy-induced alopecia was found in cisplatin (35.4%), carboplatin (94.4%), cyclophosphamide (100%), paclitaxel (100%), 5-fluorouracil (100%), doxorubicin (100%), VCR (100%).[17]

Approximately 85% of anagen effluvium occurs after chemotherapy because cells are dividing rapidly and are sensitive to cytotoxic agents.[5] Most chemotherapy agents cause alopecia due to direct toxicity hematogenously.[19] Increased blood flow around the hair follicle leads to accumulation chemotherapy agents.[16] Chemotherapy disrupt proliferation of matrix keratinocytes in the anagen bulb, turning them into the dystrophic catagen phase, and weaken hair shaft. Chemotherapy-induced alopecia is also related to premature apoptosis, p53, Fas, and c-kit factors.[8] The majority of hair will regrow after 3-6 months after chemotherapy discontinuation.[21,22]

In this study, gender and alopecia pattern were not significantly associated with chemotherapy agents. In contrast, age, ALL risk stratification, and chemotherapy phase showed a significant correlation. Sitaresmi *et al.* showed no significant difference in gender, age, and ALL risk group stratification.[13] While Yun *et al.* found no significant difference in the pattern of alopecia based on age or combination of chemotherapy agents, but gender affected the pattern of alopecia.[5]

This study found that most parents of patients did not receive counselling regarding chemotherapy-induced alopecia. Although overall (42.0%) thought alopecia was part of treatment side effects, 2.1% wanted to stop chemotherapy due to alopecia. Saraswat *et al.* found that alopecia affected social life in 72%, and 20.6% used hair accessories.[16] Alopecia may have a significant negative impact on self-confidence, body image, and QOL, especially in children.[16,23]

The limitation of this study is that the questionnaire has not been validated and questionnaire filled according to parents' assessment.

Conclusion

There is a significant correlation between chemotherapy agents and age, ALL risk stratification, chemotherapy phase, and onset of alopecia. This study can be used as reference for further research with larger samples for more generalized application. Education regarding chemotherapy-induced alopecia is important to improve QOL.

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Author's contribution

F,IS: Substantial contribution to study design, acquisition of data, manuscript writing, has given final approval of the version to be published.

SK,IAA,RN: Substantial contribution to analysis and interpretation of data, critical review, has given final approval of the version to be published.

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