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THE EFFECT OF CHEMOTHERAPY ESPECIALLY IN INDUCTIION PHASE ON OCULAR HEALTH OF ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS: AN ANALYTICAL OBSERVATIONAL STUDY

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ABSTRACT
Leukemia is one of the most common malignancies in children and eye manifestations due to leukemia in children occur more frequently in acute leukemia which can be caused by the course of the disease or by chemotherapy drugs. This study to determine correlation between chemotherapy, hemoglobin levels, platelet counts, and occurrence of ocular manifestations in pediatric leukemia patients hospitalized at Adam Malik General Hospital Medan. This study was an analytical observational study with a pre-post design and consecutive sampling involving 45 pediatric leukemia patients. Data were collected through interviews, ophthalmologic examinations, and laboratory assessments. Statistical analysis with McNemar test was performed to evaluate the association between independent variables and ocular manifestations, with a significance level of $p < 0.05$. Low hemoglobin levels and platelet counts were significantly associated with the occurrence of ocular manifestations ($p < 0.05$). However, chemotherapy was not significantly associated with the occurrence of ocular manifestations in pediatric leukemia patients ($p > 0.05$). Anemia and thrombocytopenia contribute significantly to ocular manifestations development in pediatric leukemia patients, whereas chemotherapy did not show a significant effect.

Keywords: chemotherapy; hemoglobin; ocular manifestations; pediatric leukemia; thrombocytopenia

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INTRODUCTION

Leukemia is one of the most common malignancies in children, especially in children aged 1-4 years old (Ilhan et al.,2023). The incidence of leukemia in Indonesia is mostly about 2.5-4 new cases per 100,000 children (Perdana et al.,2020). Ocular manifestations due to leukemia in children are more common in acute leukemia than chronic leukemia, and can affect all intraocular structures. The reported prevalence of eye involvement in acute leukemia ranges from 32% - 35.5% (Salloukh et al.,2022).

Eye disorders in children with acute lymphoblastic leukemia (ALL) are caused by disease course or chemotherapy drugs that can inhibit microtubule polymerization, direct axonal injury in retina, optic nerve ischemia, and loss of neurosynaptic activity. Various ocular side effects, such as cranial neuropathy manifesting as ptosis, lagophthalmos, and corneal hyperesthesia; optic atrophy, nyctalopia, and cortical blindness (Totadri et al.,2021)

Several studies have linked ocular involvement to worse prognosis (Salloukh et al.,2022). There is a correlation between ophthalmologic findings and early death within first 30 days, which patients with optic nerve or retinal ganglion cell involvement significantly associated with early death in newly diagnosed acute leukemia patients (Benvenuto et al.,2022) Therefore, a comprehensive

ocular health evaluation should be considered in all acute leukemia patients for early detection to integrate ophthalmologic examinations into the routine evaluation of all pediatric leukemia patients, particularly from the time of diagnosis, to enable early detection of structural and functional ocular changes. This study aims to analyze the effect of chemotherapy on ocular health during the induction phase of ALL

METHOD

This is an analytical observational study with a pre-post design conducted at Eye Clinic of Adam Malik General Hospital Medan. Data collection through direct eye examinations was carried out since August 2025. The study sample was ALL patients aged <18 years old who underwent chemotherapy at Adam Malik General Hospital Medan. The sampling technique used was consecutive sampling.

Inclusion criteria for this study were patients diagnosed with ALL based on bone marrow aspiration, aged <18 years old, and undergoing induction chemotherapy. Patients who were uncooperative during eye examinations, those with incomplete data, those who died, and those lost to follow-up before completing induction chemotherapy were excluded. Data were collected from patient registries and medical records, including age at diagnosis and gender at Pediatric Hemato-Oncology Clinic. Eye examinations were performed by an ophthalmologist and eye manifestations were recorded.

Statistical analysis

Data were analyzed using Mc Nemar and then presented in narrative, tabular, or graphical form. All categorical data were presented as frequency and percentage values. Numerical data were presented as mean and standard deviation for normally distributed data, while non-normally distributed data were presented as median, minimum, and maximum values. The McNemar test was used to analyze the presence or absence of eye manifestations before and after induction chemotherapy. The significance level was $p < 0.05$. This research has been approved by the ethics committee with reference number 787/KEPK/USU/2025

RESULT

This study included 45 pediatric patients with ALL undergoing induction chemotherapy at Haji Adam Malik General Hospital, Medan. Most patients were male (60%) and well-nourished (60%). Mean patients age was 6.18 $\pm$ 4.11 years, mean body height was 110.96 $\pm$ 24.99 cm, and mean body weight was 19.89 $\pm$ 12.07 kg. (Table 1)

Table 1.
Characteristics of research subjects (n= 45)

Characteristics	n = 45
Gender, n (%)	
Male	27 (60)
Female	18 (40)
Age (years)	
Mean	6,18 ± 4,11
Median (min – max)	5 (1 – 17)
Height (cm)	
Mean	110,96 ± 24,99
Median (min – max)	105,5 (71-170)
Weight (kg)	
Mean	19,89 ± 12,07
Median (min – max)	15 (7 – 59)
Nutritional Status, n (%)	
Normal	27 (60)
Undernourished	9 (20)
Severely Malnourished	7 (15,6)
Overweight	2 (4,4)

Before induction chemotherapy, patients had moderate to severe anemia, with a mean hemoglobin level of 7.38 ± 2.96 g/dL (median 7.9 g/dL; range 2.1–12.6 g/dL). Following induction chemotherapy, hemoglobin levels improved, with a mean of 9.05 ± 2.65 g/dL (median 8.9 g/dL; range 1.7–11.8 g/dL), indicating hematologic recovery in most patients (Table 2).

Platelet counts were markedly reduced before chemotherapy, with a mean of 69.1 × 10^3/µL and a median of 21 × 10^3/µL (range 4–676 × 10^3/µL), reflecting severe thrombocytopenia in many patients. After induction chemotherapy, platelet counts improved, reaching a mean of 219.9 × 10^3/µL and a median of 199 × 10^3/µL (range 2–706 × 10^3/µL), indicating recovery from thrombocytopenia in most patients (Table 2).

Table 2.
Laboratory test results before and after chemotherapy

Laboratory Results	Chemotherapy	
	Before (n = 45)	After (n = 45)
Hemoglobin (g/dL)		
Mean	7,38 ± 2,96	9,05 ± 2,65
Median (min – max)	7,9 (2,1 – 12,6)	8,9 (1,7 – 11,8)
Mild Anemia	6 (13,3)	14 (31,1)
Moderate Anemia	16 (35,5)	18 (40)
Severe Anemia	23 (51,1)	13 (29,9)
Platelet (x10^3/µL)		
Mean	69,1 ± 47,09	219,931 ± 203,336
Median (min – max)	21 (4-676)	21 (2-706)
Mild thrombocytopenia	1 (2,2)	1 (2,2)
Moderate thrombocytopenia	8 (17,7)	1 (2,2)
Severe thrombocytopenia	34 (75,6)	17 (37,7)
Thrombocytosis	2 (4,4)	2 (4,4)
Leukocytes, n (%)		
> 50 x10^3/µL	9 (20)	2 (4,4)
≤ 50 x10^3/µL	36 (80)	43 (95,6)

Based on leukocyte counts before chemotherapy, most patients (36 children, 80%) had leukocyte counts ≤ 50,000/µL. Similarly, after chemotherapy, most patients (43 children, 95.6%) had leukocyte counts ≤ 50,000/µL, which is prognostically associated with a higher risk. Overall, the laboratory profile after induction chemotherapy is consistent with the clinical improvement of ALL. (Table 2). Overall, the results of this study indicate clinical improvement in ocular health after chemotherapy, although this change did not reach statistical significance (p = 0.083). (Table 3)

Table 3.
Ocular Examination Results Before and After Chemotherapy

Ocular Manifestations	Chemotherapy		
	Before	After	*P value*
Normal	33 (73,3)	38 (84,5)	0,083*
Conjunctival hemorrhage	6 (13,3)	3 (6,6)	
Conjunctivitis	3 (6,7)	1 (2,2)	
Leukemic optic neuropathy	3 (6,7)	3 (6,7)	

**Marginal homogeneity*

The marginal homogeneity test showed a p-value of 0.083, indicating no statistically significant difference between ocular manifestations before and after chemotherapy. However, a p-value approaching the significance limit indicates a trend toward positive clinical changes, which would likely become significant with longer observation periods or larger sample sizes. (Table 3)

Furthermore, the lack of a statistically significant relationship may be influenced by several factors, including predominance of normal eye conditions from basline study, relatively small number of ocular manifestations cases, and largely mild and reversible nature of ocular manifestations. This

confirms that chemotherapy is not the primary cause of ocular disorders but rather plays an indirect role through controlling leukemia activity and improving the patient's systemic condition.
Overall, this table indicates that induction chemotherapy in children with ALL tends to have a positive impact on ocular health, although this effect was not sufficiently strong to be statistically proven in this study. Therefore, ophthalmological monitoring is still necessary, especially in patients with early ocular manifestations or a high risk of ocular complications.

DISCUSSION

Ocular manifestations in leukemia are an important clinical complication because eyes can be the site of direct or indirect involvement by leukemic process. This study found a significant proportion of patients with ocular involvement, particularly during the early stages of diagnosis and chemotherapy induction. This is consistent with evidence that ocular involvement in leukemia can appear at various stages of the disease course and may even be the first clue before a systemic diagnosis of leukemia is established (Salloukh et al.,2022; Benvenutio et al., 2022; Hafeez et al., 2020).

The pathophysiology of ocular manifestations in leukemia is multifactorial. Ocular involvement can occur through three main mechanisms: direct infiltration of leukemic cells into ocular tissue, hematologic complications such as anemia and thrombocytopenia, and side effects of chemotherapy that affect eye structure and function (Salloukh et al.,2022; Hafeez et al., 2020).

Blast cell infiltration can occur in the retina, choroid, optic nerve, and even the orbit. Indirect mechanisms primarily cause retinal hemorrhages, retinal vein dilation, and retinal edema due to impaired hemostasis and blood hyperviscosity (Terwilliger et al., 2021).

These results support the findings of various studies that retinal manifestations are the most common form of ocular involvement. The retina has a rich vascular supply and is a highly sensitive structure to changes in blood flow and hematologic disorders. Hyperviscosity due to high leukocytosis and severe thrombocytopenia contributes to retinal hemorrhages and papilledema (Benvenutio et al., 2022). In some cases, optic nerve involvement in the form of optic neuritis or direct infiltration can lead to progressive visual acuity loss and can be irreversible if not treated promptly.

In addition to retinal features, this study also found ocular complaints such as pain, redness, decreased visual acuity, diplopia, and periorbital edema. These complaints are still frequently reported in patients with acute lymphoblastic leukemia, particularly in those with central nervous system involvement or severe leukostasis (Benvenutio et al., 2022). These manifestations can lead to orbital involvement and increased intracranial pressure, which directly impact the optic nerve.

Ocular involvement in leukemia not only impacts visual morbidity but also has prognostic value. Several literatures indicate an association between the presence of ocular manifestations and a higher disease burden, the risk of CNS involvement, and a higher relapse rate (Benvenutio et al., 2022; Seiter et al., 2024; Alagio et al., 2022) Therefore, ophthalmological observation should not be neglected during the monitoring and treatment of leukemia patients.

In this study, the occurrence of ocular manifestations demonstrates the urgency of early detection and multidisciplinary management. Regular ocular examinations—including fundoscopy and visual acuity assessment—are necessary, especially in patients with high leukocytosis, severe anemia, thrombocytopenia, or visual symptoms. Timely intervention can prevent further damage to ocular structures and maintain patients' quality of life during therapy.

The effects of chemotherapy on the eyes in pediatric leukemia patients can be direct due to drug toxicity, or indirect through hematologic changes or infectious complications (Ilhan et al.,2023; Perdana et al.,2020). In this study, it was found that most patients undergoing chemotherapy still exhibited ocular manifestations, although these varied depending on the treatment phase and level of disease control.

Physiologically, regression of ocular manifestations such as retinal hemorrhages can occur after a good response to chemotherapy; this reflects improvement in thrombocytopenia and retinal vascular stability. Chemotherapy can rapidly reduce the number of blast cells, reduce the risk of leukostasis and hyperviscosity, thereby reducing microvascular pressure that previously played a role in intraocular hemorrhage occurrence (Murkit et al., 2024; Mathew et al., 2021). Therefore, the success of chemotherapy has the potential to have a positive impact on the improvement of ocular manifestations directly related to leukemia disease activity. However, chemotherapy can also have toxic effects on eye structure, depending on drug type used. Several cytotoxic agents, such as methotrexate, cytarabine, and vincristine, are known to be associated with ocular changes including conjunctivitis, keratitis, optic neuritis, and toxic retinopathy (Hafeez et al., 2020; Terwilliger et al., 2021). In some patients, especially those receiving intrathecal chemotherapy, toxic effects on the optic nerve or retina can worsen pre-existing visual impairment. In addition, immunosuppression due to chemotherapy makes patients more susceptible to opportunistic infections such as retinitis, which can permanently threaten visual function if not treated quickly (Murkit et al., 2024; Mathew et al., 2021; Duran et al., 2024).

Pathophysiologically, chemotherapy works by eliminating leukemia cells in bone marrow, which is ultimately expected to restore normal hematopoietic function. This improvement is reflected in increased hemoglobin levels, normalization of platelet counts, and a decrease of abnormal leukocytes. In this study, although chemotherapy was not directly associated with a decrease in the incidence of ocular manifestations, chemotherapy played a significant role in modifying hematological factors that have been shown to be closely associated with ocular abnormalities (Murkit et al., 2024; Mathew et al., 2021).

Changes in hemoglobin levels are an important indicator in assessing the indirect impact of chemotherapy on ocular manifestations. In leukemia, anemia can occur due to several mechanisms: inhibition of erythrocyte production by leukemia cells in bone marrow, hemolysis, and bleeding due to thrombocytopenia (Salloukh et al.,2022). Chronic hypoxia increases the permeability of retinal vascular endothelium and leads to microvascular fragility. This can lead to retinal hemorrhages, flame-shaped hemorrhages, white-centered hemorrhages (Roth spots), and cotton wool spots, which are often found on fundoscopy (Hafeez et al., 2020; Terwilliger et al; Laimon et al., 2024). Similarly, anemia can also exacerbate hyperviscosity in cases of extreme leukocytosis as part of leukostasis, further compromising retinal perfusion (Laimon et al., 2024; Mandonca et al., 2021; Athwal et al., 2024). The results of this study indicate that low hemoglobin levels are significantly associated with the occurrence of ocular manifestations. Therefore, improving hemoglobin levels after chemotherapy has the potential to reduce ocular complications risk, although this effect is not always immediately apparent during the induction phase of therapy.

In addition to hemoglobin, platelet levels also play a crucial role in the development of ocular manifestations, particularly intraocular hemorrhage. The severity of retinal hemorrhage is directly proportional to the level of platelet decline, that platelets $\leq 50{,}000/mm^3$ significantly increases the risk of retinal hemorrhage in leukemia patients, especially in acute leukemia (Benvenutio et al). Low platelet levels result in increased fragility of blood vessel walls therefore more susceptible to rupture, especially in retinal vessels that have a thin microvascular structure and are sensitive to changes in intravascular pressure (Terwilliger et al., 2021; Laimon et al., 2024; Mandonca et al., 2021). Intravascular pressure itself can increase in conditions of hyperviscosity due to extreme

leukocytosis that often accompanies leukemia, therefore bleeding risk becomes greater (Totadri et al.,2021). In this study, low platelet levels showed a significant association with ocular manifestations. In the early phase of chemotherapy, the myelosuppressive effect can cause persistent or even more severe thrombocytopenia, therefore risk of ocular hemorrhage remains high even though chemotherapy has been given. This may explain why chemotherapy does not appear to have a direct protective effect on ocular manifestations statistically.

This study found no significant association between induction chemotherapy and the incidence of ocular disorders in pediatric patients with ALL. This finding can be explained by several clinical and methodological considerations. First, mostly ocular manifestations in childhood leukemia are secondary to disease activity and hematologic changes, such as anemia and thrombocytopenia, rather than a direct effect of chemotherapy agent. Second, induction chemotherapy primarily aims to suppress leukemia cell proliferation and improve hematologic conditions. Third, the relatively short observation period during induction phase of chemotherapy may limit the study's ability to detect chemotherapy-induced ocular side effects. Fourth, the limited sample size and low variation in post-chemotherapy ocular manifestations may have led to insufficient statistical power to demonstrate a significant association between chemotherapy and eye disorders. Thus, this study results indicate that chemotherapy is not a primary independent factor influencing ocular disorders incidence in children with ALL, but rather plays an indirect role through improvements in disease activity and hematologic profiles.

Although chemotherapy did not demonstrate a statistically significant association with the incidence of ocular manifestations in this study, chemotherapy still plays a fundamental role in overall leukemia control. The success of chemotherapy in achieving remission and improving hematologic profile in the long term is expected to have a positive impact on improving ocular manifestations directly related to disease activity. In other words, chemotherapy contributes to the improvement of ocular manifestations indirectly through the normalization of hemoglobin, platelets, and leukocytes, rather than as an independent factor. Chemotherapy works by eliminating leukemic cells in the bone marrow, thereby facilitating the restoration of normal hematopoietic function. This recovery is reflected by increased hemoglobin levels, normalization of platelet counts, and a reduction in abnormal leukocyte counts. In the present study, although chemotherapy was not directly associated with a decreased incidence of ocular manifestations, it played an important role in modifying hematologic factors that were found to be closely associated with ocular abnormalities. (Murkit et al.,2024; Mathew at al.,2021)

Overall, chemotherapy for leukemia has a two-pronged effect on eye: (1) Improvement of ocular manifestations through better disease control, and (2) the risk of toxic or secondary ocular complications due to immunosuppression. A multidisciplinary approach involving hematology-oncology and ophthalmology specialists is essential to minimize the negative impact of chemotherapy on vision without compromising the effectiveness of therapy.

CONCLUSION

Anemia and thrombocytopenia contribute significantly to development of ocular manifestations in children with leukemia, whereas chemotherapy did not show a significant effect. Nevertheless, successful chemotherapy may have a positive impact on improving ocular manifestations through better control of leukemia disease activity.

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