FACTORS RELATED TO INCIDENCE OF ANEMIA IN HIV INFECTED CHILDREN WITH ZIDOVUDIN IN H ADAM MALIK GENERAL HOSPITAL

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ABSTRACT

Background: Anemia is one of the most common haematological complications in people with HIV infection. Anemia is associated with increased disease progression as well as worsening clinical conditions. Zidovudin is the first-line anti-retoviral treatment of HIV which has anemia side effects. The prevalence of anemia due to zidovudine varies from 3.7% to 41.6%, 21.3% was moderate-severe anemia. Besides zidovudin, there was a relationship between age, CD4 cell count, and opportunistic infections with the incidence of anemia.

Objective: To study factors related to incidence of anemia in HIV infected children with zidovudin in H Adam Malik general hospital.

Methods: A retrospective cross-sectional study, 80 subjects who received zidovudin therapy were taken through medical records, then analyzed bivariate and multivariate analysis of risk factors for anemia.

Results: The incidence of anemia was 41.4% consisting of mild anemia 28.6%, moderate anemia 5.7%, severe anemia 7.1%. There is a correlation between anemia and immunodiciency status (P <0.001, PR 12.833, CI 1.863 - 88.395), nutritional status (P <0.001, PR: 10.731, CI 2.763 - 41.671), and length of therapy (P = 0.001, PR 2.779, CI 1.428 - 5,409). Multivariate analysis found that nutritional status was the most influential risk factor in influencing the onset of anemia in children with HIV who were given zidovudine therapy.

Conclusion: there is a relationship between nutritional status, immonodeficiency status and length of therapy to the incidence of anemia in HIV-infected children who are given zidovudine therapy.

Key Words: anemia, HIV, zidovudin, nutritional status, immonodeficiency

BACKGROUND

Human Immunodeficiency Virus (HIV) infection is a disease caused by infection HIV virus.[1] Human Immunodeficiency Virus attacks the body's immune system by infecting and destroying T-lymphocytes, making them susceptible to infection. Uncontrolled HIV infection will lead to an immune deficiency syndrome called Acquired Immune Deficiency Syndrome (AIDS). Acquired immune deficiency syndrome caused by HIV infection which characterized by a variety of clinical symptoms, including severe immunodeficiency with opportunistic infections and malignancies, and degeneration of the central nervous system.[2]

Anemia is one of the most common hematological complications found in children with HIV infection. Anemia is associated with increased disease progression and worsening clinical conditions. The mechanism of anemia in HIV infection caused by the inefficient process of hematopoiesis, due to malnutrition, coinfection, neoplasm, decreased production of erythropoietin and the use of antiretroviral drugs (ARV).[3] The prevalence of anemia in HIV infection ranged from 60.5%.[4] In Jakarta, it was reported that there were 13.7% anemia in patients receiving zidovudine. In Hasan Sadikin Hospital, there were 41.6% patient suffer from anemia which 21.3% were moderate-severe anemia due to zidovudine.[5] In 2013 it was reported in Asia that 2.9% of severe anemia occurred after six months of taking ARV containing zidovudine.[6]

Besides zidovudine, there are relationship between age, CD4 levels, opportunistic infections, nutritional status, and drugs used by HIV patient to the incidence of anemia. Zidovudine is the first-line ARV used in HIV patients in Indonesia, but very often causes anemia, however the data of prevalence of anemia in children due to the use of zidovudine in HIV infection in Indonesia have not been widely reported.

The purpose of this study was to determine the factors associated to the incidence of anemia in children with HIV who received zidovudine at RSUP H Adam Malik.

METHOD

This study is an analytic observational study with a retrospective cross-sectional design to determine the relationship between age, gender, duration of therapy, CD4 levels, the presence of opportunistic infections, nutritional status, and other drugs to the incidence of anemia in children with HIV who received zidovudine. We analyzed medical record from outpatient clinic of Pediatric Allergy Immunology RSUP HAM Medan from January 2014 until November 2020. Bivariate analysis using Chi-square test and Fischer's test as an alternative test. To find out the most important factor, logistic regression analysis is used. This research has been approved by the Research Ethics Committee of the University of North Sumatra no: 752/KEP/USU/2020.

RESULT

This study consisted of 70 medical records of outpatient HIV patients at the allergy immunology clinic. Data were available for 70 HIV infected children in medical record from outpatient clinic of Pediatric Allergy Immunology RSUP HAM Medan from January 2014 until November 2020. The proportion of gender between male and female are almost equal (51,4% and 48,6%). Subjects

aged 5 - < 12 years amounted to 43 people (61.4%). The median initial age of child subjects receiving zidovudine therapy was 56 months with the youngest initial age being 6 months and the oldest being 158 months. full characteristics are presented in table 1

Table 1 Characteristics of Research Subjects

Characteristics	**n = 70**
Gender, n (%)	
Male	36 (51,4)
Female	34 (48,6)
Age (years), n (%)	
< 5	12 (17,1)
5 – < 12	43 (61,4)
12 – 16	15 (21,4)
Initial Age receiving Zidovudin, months	
Median (min – max)	56 (6 – 158)
Parents occupation, n (%)	
Housewife	5 (7,10)
Private employees	2 (2,9)
Pension	1 (1,4)
Farmer	6 (8,6)
civil servant	4 (5,7)
Police	1 (1,4)
Driver	1 (1,4)
entrepreneur	41 (58,6)
Etc	9 (12,9)
Cared by, n (%)	
family	10 (14,3)
Parents	46 (64,3)
Foundation	15 (21,4)
Parent HIV status, n (%)	
Both parents	46 (65,7)
Mother	6 (8,6)
Unknow	18 (25,7)
Delivery status, n (%)	
Normal	49 (70)
Sectio caesarian	5 (7,1)
Unknow	16 (22,9)
immune deficiency status, n (%)	
Mild	13 (18,6)
Moderate	8 (11,4)
Severe	27 (38,6)
No deficiency	22 (31,4)
Nutritional status, n (%)	
Severe malnourish	15 (21,4)
Mild malnourish	24 (34,3)
Good nutritional status	31 (44,3)
Opportunistic Infections, n (%)	
Bronchitis	1 (1,4)
Bronchitis, skin tuberculosis	1 (1,4)
Bronchopneumonia	3 (4,3)
Candidiasis, Tuberculosis	2 (2,9)
Citomegalovirus	1 (1,4)
Lymphadenitis Tuberculosis	2 (2,8)
Pneumocystis pneumonia	1 (1,4)
Rubella	1 (1,4)
pulmonary TB	23 (32,9)
skin fungus	1 (1,4)
No Opportunistic Infections	34 (48,6)

Other Drugs, n (%)	
Isoniazid	20 (28,6)
Co-trimoxazole	12 (17,1)
Co-trimoxazole and isoniazid	8 (11,4)
Co-trimoxazole and ganciclovir	2 (2,9)
Do not use other drugs	28 (40)
Duration of Zidovudine Therapy, n (%)	
> 6 months	36 (51,4)
6 months	34 (48,6)

Table 2 shows the frequency distribution of anemia in children with HIV who received zidovudine therapy. The frequency of children with mild anemia was 28.6%, moderate anemia 5.7%, and severe anemia was 7.1%.

Table 2. Distribution of the Frequency of Anemia

Incidence of Anemia	**n (%)**
Mild Anemia	20 (28,6)
Moderate Anemia	4 (5,7)
Severe Anemia	5 (7,1)
No Anemia	41 (58,6)

Subjects with immune deficiency status were 28 children (58.3%) with anemia, meanwhile subjects with good immune status only 1 child (4.5%) had anemia. There was a significant relationship between immune deficiency status to the incidence of anemia (p<0.001) with Prevalence Ratio (PR) was 12.833 (95% CI 1.863 – 88.395). Subjects with malnutrition status, there were 27 children (69.2%) with anemia, while the subjects with good nutritional status, only 2 children (6.5%) with anemia. There was a significant relationship between nutritional status to the incidence of anemia (p<0.001) with PR was 10,731 (95% CI 2,763 – 41,671). Subjects with duration of therapy less than 6 months, there were 21 children (61.8%) with anemia, while the subjects with the duration of therapy more than 6 months, there were 8 children (22.2%) with anemia. There was a significant relationship between the length of therapy with zidovudine to the incidence of anemia (p = 0.001) with PR was 2,779 (95% CI 1,428 – 5,409). Full bivariate analysis of risk factors for anemia in children with HIV who received zidovudine therapy are presented in table 2

Table 3 Bivariate Analysis of Anemia in Children with HIV who Received Zidovudine Therapy

Subject Characteristics	**Incidence of Anemia**		**p**	**PR**
	Yes (n=29)	**No (n=41)**		**(95% CI)**
Gender, n (%)				
Men	15 (41,7)	21 (58,3)	0,967[a]	1,012
Women	14 (41,2)	20 (58,8)		(0,579-1,767)
Age, n (%)				
< 5 years	7 (58,3)	5 (41,7)	0,215[b]	1,538
5 years	22 (37,9)	36 (62,1)		(0,861-2,748)
Immune Deficiency, n (%)				
Yes	28 (58,3)	20 (41,7)	<0,001[a]	12,833
No	1 (4,5)	21 (95,5)		(1,863-88,395)
Nutritional Status, n (%)				
Malnutrition	27 (69,2)	12 (30,8)	<0,001[a]	10,731
Good Nutrition	2 (6,5)	29 (93,5)		(2,763-41,671)
Pneumonia, n (%)				

Yes	4 (66,7)	2 (33,3)	0,224[b]	1,707
No	25 (39,1)	39 (60,9)		(0,897-3,247)
CMV, n(%)				
Yes	2 (100)	0	0,168[b]	2,519
No	27 (39,7)	41 (60,3)		(1,897-3,376)
Pulmonary TB, n (%)				
Yes	12 (42,9)	16 (57,1)	0,843[a]	1,059
No	17 (40,5)	25 (59,5)		(0,603-1,860)
Gangcyclovir, n (%)				
Yes	1 (50)	1 (50)	1,000[b]	1,214
No	28 (41,2)	40 (58,8)		(0,295-4,997)
Co-trimoxazole, n (%)				
Yes	12 (54,5)	10 (45,5)	0,131[a]	1,540
No	17 (35,4)	31 (64,6)		(0,898-2,642)
INH				
Yes	12 (42,9)	16 (57,1)	0,843[a]	1,059
No	17 (40,5)	25 (59,5)		(0,603-1,860)
Duration of Zidovudine Therapy, n (%)				
6 months	21 (61,8)	13 (38,2)	0,001[a]	2,779
> 6 months	8 (22,2)	28 (77,8)		(1,428-5,409)

[a]Chi Square, [b]Fischer's Exact

Multivariate analysis in this study uses multiple logistic regression because the dependent variable is categorical. Based on the value of Exp (B) shows that the independent variable which is the most dominant risk factor in influencing the incidence of anemia in children with HIV who are given zidovudine therapy is nutritional status with a value of 26,207 (95% CI = 4,888 - 140,520) meaning that children with HIV with Poor nutritional status tend to be at risk for anemia by 26.207 times greater than children with HIV with good nutritional status. Meanwhile, based on immunodeficiency, children with HIV with immune deficiency status tend to be at risk to developing anemia by 21,633 times greater than children with HIV with normal immune status.

DISCUSSION

The incidence of anemia in this study was 41.4%, consist of 28.6% mild anemia, 5.7% moderate anemia and 7.1% severe anemia. Similar result with Sumantri at Hasan Sadikin Hospital founded that the prevalence of anemia was 41.6%, where 35.2% mild anemia, 5.2% anemia moderate, and 1.1% severe anemia.[5] The incidence of anemia in this study was higher than the Ethiopian study where the overall incidence of anemia was 10.5 per 100 children per year of observation.[7] Anemia in HIV caused by decreased production of red blood cells, increased destruction of red blood cells, and ineffective production of red blood cells.[8]

There was no significant relationship between age and to the incidence of anemia in this study. Anemia was more common in the age group < 5 years (58.3%) than children aged 5 years (37.9%). This happens because at the age of toddlers experiencing a phase of rapid growth, at this stage will require reserves of iron, folic acid and vitamin B12 to help the growth process, if not given adequate nutritional intake it will result in decreased hemoglobin levels and cause anemia.[9] Masresha's study on HIV patients taking ARVs found that the incidence of anemia was 72.4% at the age of 5 years.[7] According to the 2016 Ethiopian Demographic Health Survey Report, the prevalence of anemia in

Ethiopia in under-fives was 56% while antiretroviral-related anemia in this age group ranged from 18, 9% to 30%.[10]

In this study, the incidence of anemia was almost the same in boys and girls (41.7% and 41.2%). The same results were obtained by Enegwaw in Ethiopia that the incidence of anemia in boys and girls was 14.9% and 17.6%.[11] In contrast to Cahyani's research at Sanglah Hospital, Denpasar, it was found that more boys had anemia than girls (69%: 31%).[12] The results of this study are similar to the results of a study conducted by Leite in Brazil that boys showed a slightly higher risk of anemia than girls (PR 1.06; 95% CI 1.01- 1,13).[9] On the other hand, Sharma's study in India found that girls had a greater risk factor for anemia than boys.[13] In several studies, it can be seen that gender and anemia have a less consistent relationship, where there are several studies that reveal a relationship and some also do not show a relationship between these variables.

The use of zidovudine in some people may experience several side effects, one of them are decrease in hemoglobin level which is influenced by the duration of therapy. The higher dose of the drug used, the more severe of side effects, it can also be reviewed with the length of use of the drug. If the breakdown of the drug in the blood is slower than normal, the blood level of the drug will be higher, and this is more likely to cause side effects. Zidovudine tends to suppress red blood cells or inhibit the growth of hematopoietic cells in the bone marrow of AIDS patients, resulting in a decrease in hemoglobin level.[10] In this study, subjects who received zidovudine < 6 months had a risk of 2,779 times (95% CI 1,428-5,409) to suffer from anemia compared to those who received zidovudine > 6 months. Similar result with Kaibalaya's study, where the average duration of Hb decline was 3.56 ± 2.43 months.[15]

In this study, there was a significant relationship between immune deficiency status and the incidence of anemia ($p<0.001$, PR 12.833, CI 1.863 – 88.395). Similar findings were found in research from Nepal where the prevalence of anemia increased significantly with a decrease CD4 cell count (95% CI; 1.23- 6.77).[11] Severe immunosuppression may lead to viral duplication, which can lead to anemia, this is exacerbated by increased myelosuppression mediated by cytokines and opportunistic infections due to the failure of the immune system to inhibit viral replication.[8] In contrast to the study in Nigeria that hemoglobin values were not associated with CD4 levels ($P = 0.302$), so hemoglobin could not be used as a predictor of immune status (OR 1.461, 95% CI 0.866 - 2,464, $P = 0.16$).[17]

Undernourished children were 2.8 times more likely to develop anemia than children with normal nutritional status (PR 2.7 95% CI 1.5-5) during the follow-up period.[7] In this study there was a significant association between nutritional status with the incidence of anemia ($p<0.001$) and the value of the PR obtained was 10.731 (95% CI 2.763 – 41.671).

Cotrimoxazole use in zidovudine associated anemia may be explained by the fact that cotrimoxazole, not only has a myelosuppressive effect, but also can reduce renal clearance of zidovudine resulting increasing plasma levels of zidovudine and subsequently increased toxicity.[18] In this study, there was no significant association between cotrimoxazole use with the incidence of anemia ($p = 0.131$). The same result found in the Berhane study in Ethiopia, there was no difference in the incidence of anemia in subjects receiving cotrimoxazole prophylaxis in the group receiving zidovudine and the control group.[19] On the other hand, Cahyani's study in Denpasar, reported the proportion of

children who received cotrimoxazole therapy had more anemia than those who did not receive cotrimoxazole (92%: 8%).[12]

A study in Iran found a relationship between the use of anti-tuberculosis drugs (INH) to the incidence of anemia (OR 4.3, CI: 1.788–10.470) and the administration of INH and vitamin B6 was a protective effect against anemia (OR 0.3, CI: 0.146–0.842. In this study there was no significant relationship between the use of INH to the incidence of anemia (p=0.843), INH caused an increase in the excretion of pyrodoxine (vitamin B6) which is needed for heme synthesis, so that vitamin B6 deficiency causes sideroblastic anemia.[20]

Gancyclovir is a drug used to treat cytomegalovirus infections. This infection is one of the most common opportunistic infections in HIV/AIDS patients. In this study, there was no significant relationship between the use of gancyclovir to the incidence of anemia (p=1,000). Similar results were found with study in Iran where gancyclovir could inhibit progenitor cells based on the concentration gradient of gancyclovir and granulocyte and erythroid progenitor cells (P=0.117, OR: 0.785, CI 0.077–7.961).[14]

Several opportunistic infections can cause anemia through direct infiltration of bone marrow such as cytomegalovirus, parovirus B19, Mycobacterium and Cryptococcus neoformans infections.[21] In this study, there was no significant relationship between CMV infection to the incidence of anemia (p=0.168), pneumonia infection to the incidence of anemia (p=0,224) and pulmonary TB infection to the incidence of anemia (p=0,843). The same results were obtained by Sumantri at Hasan Sadikin Hospital in Bandung, where tuberculosis infection had no effect to the incidence of anemia (p = 0.83).[5] Unlike Masresha's study in Ethiopia, tuberculosis infection had 2.1 times higher risk of anemia than without tuberculosis (OR = 2.1, 95% CI 1.4, 3.3).[7]

The cause of anemia in tuberculosis due to suppression of erythropoiesis by inflammatory mediators, IL-6, IFN-γ, IL-1β, TNF-α. The pathogenesis of anemia due to inflammation occurs due to invasion of microorganisms, malignant cells or autoimmune reactions causing T cell activation (CD3+) and monocytes. These cells induce immune effector mechanisms by producing cytokines such as interferon-γ from T cells and TNF-, Interleukin-1, Interleukin-6 and Interleukin-10 (from monocytes or macrophages). These proinflammatory cytokines cause inhibition of proliferation and differentiation of erythroid progenitor cells and trigger suppression of erythropoietin in the kidney. Interleukin-6 and lipopolysaccharide stimulate the expression of the acute phase protein hepcidin, which reduces the absorption of iron in the duodenum. Hepcidin is elevated during inflammation and infection. This results in iron dysregulation with hypoferremia and anemia due to inflammation.[22]

CONCLUSION

Based on the results of this study it can be concluded that there is a relationship between nutritional status, immunodeficiency status and duration of therapy to the incidence of anemia in HIV-infected children given zidovudine therapy. There was no relationship between the initial age of zidovudine administration, gender, opportunistic infection and other drugs used to the incidence of anemia in HIV-infected children who were given zidovudine therapy.

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