ANALYSIS OF ADRENAL SUPPRESSION AFTER HIGH DOSE PREDNISONE THERAPY ON CHILDREN WITH STANDARD RISK ACUTE LYMPHOBLASTIC LEUKEMIA IN INDUCTION AND CONSOLIDATION PHASE

ANALYSIS OF ADRENAL SUPPRESSION AFTER HIGH DOSE PREDNISONE THERAPY ON CHILDREN WITH STANDARD RISK ACUTE LYMPHOBLASTIC LEUKEMIA IN INDUCTION AND CONSOLIDATION PHASE

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ABSTRAK

Glukokortikoid memegang peran penting dalam terapi pasien LLA menyebabkan apoptosis pada sel limfoblastik. Pasien LLA risiko biasa mendapatkan dosis tinggi prednison. dosis suprafisiologis dari prednison dapat mensupresi aksis hipotalami pituitari. Hal ini dapat menurunkan ketahanan tubuh anak LLA terhadap infeksi dikarenakan penurunan kadar kortisol. Kejadian supresi adrenal di Indonesia masih belum diteliti pada pasien LLA pada fase induksi hingga fase konsolidasi. Tujuan penelitian untuk menganalisis perubahan kadar kortisol sebagai gambaran supresi adrenal pada pasien anak LLA risiko biasa di fase induksi dan konsolidasi pasca mendapatkan prednison dosis tinggi jangka panjang. Penelitian dengan desain prospektif observasional longitudinal, penelitian dilakukan dengan pencatatan hasil laboratorium pemeriksaan darah (kortisol) pasien LLA yang memenuhi kriteria inklusi mendapatkan terapi prednisone selama fase induksi. Pengambilan darah dilakukan selama fase induksi dan konsolidasi pada minggu ke-0,4,5,6,7,8,10,12 pada protokol kemoterapi LLA Indonesia 2013. Jumlah sampel yang didapat 13 pasien (laki-laki 8, perempuan 5). Penurunan kadar kortisol setelah terapi prednisone terjadi pada minggu ke-10 dengan presentase penurunan 53% terhadap kadar kortisol minggu ke-0 (p=0,027). Dan terjadi peningkatan 64% pada minggu ke-12 terhadap minggu ke-10 (p=0,003). Prednison tidak menyebabkan supresi adrenal pada fase induksi, penurunan kadar kortisol pada fase konsolidasi bersifat sementara. ***(FMI 2018;54:59-63)***

Kata kunci*: Leukemia limfoblastik akut risiko biasa; kadar kortisol; supresi adrenal, kemoterapi fase induksi; kemoterapi fase konsolidasi*

ABSTRACT

Prednisone has an important role in the therapy of patient with standard risk ALL. Patients with standard risk ALL receiving high dose prednisone as therapy and supraphysiology dose of prednisone are expected to cause suppression in HPA-axis (Hypothalamic Pituitary Adrenal axis). This suppression could reduce immune system in children with ALL and increase infection risk because reduction of cortisol level. In Indonesia, we did not find study about the incident of adrenal suppression after high dose prednisone therapy, especially in induction to consolidation phase ALL patient. The aim of this study was to analyze adrenal suppression after high dose prednisone therapy on children with standard risk acute lymphoblastic leukemia in induction and consolidation phase. This study has received a certificate of Ethical Clearance No. 588/Panke.KKE/X/2016, a longitudinal observational, prospective, non-randomized trial involving children with ALL who received prednisone for 49 days during the induction phase. We collected and compared laboratory result of cortisol level in children with ALL and received prednisone therapy during induction to consolidation phase. Sample was taken at week 0,4,5,6,7,8,10,12 in the course of ALL chemotheraphy Indonesian protocol year 2013. Serum was examined using methods CLIA ADVIA Centaur® XP. Between June 2016 – January 2017, 13 patients (8 males, 5 females) were included in this study. Decrease of cortisol level after prednisone therapy occured in week-10 as much as 53% compared with week-0 (p=0.027). Cortisol level increased 64% of week-12 compared with week-10 (p=0.003). In conclusion, high dose prednisone is not significant to causing adrenal suppression in induction phase of ALL patients, and the reducing cortisol level is reversible. ***(FMI 2018;54:59-63)***

Keywords*: Standard risk acute lymphoblastic leukemia; cortisol levels; adrenal suppression; prednisone; induction phase chemotherapy; consolidation phase chemotherapy*

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INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is a malignancy which develops from lymphoid cell precursor (Lanzkowski 2011). For several periods ALL therapy has developed succesful improvement with use chemotherapy agent as therapy (Christensen et al 2005). Some protocols include steroid as an immunosupressant and in several studies show increased mortality and occurrence

of infection because of the side effect from chemo-therapy and high dose steroid therapy.

ALL patients have high mortality rate as a result of infection which occur because adrenal insufficiency in patients with high dose steroid therapy, so that in protocol it is recommended to tapering off the dose of steroid (Ansari et al 2014). Besides, glucocortioid suppresses adrenal fuction and reduces immune system of the body against infection (Shulman et al 2007). A study conduted by Conter et al (2009) showed the mortality in induction phase was about 1.6%. Another study by Prucker et al (2009) stated that 31 (3.4%) out of 396 patients died in induction phase and first complete remission. Another study showed 1.0%-1.3% average mortality in inducton phase (Pui 2000, Christensen et al 2005). Whereas, mean result of mortality in first complete remission is between 1.6%-3% (Silverman et al 2000, Pui 2000, Christensen et al 2005, Conter et al 2009, Prucker et al 2009). In Indonesia, we did not find any study about the incident of adrenal suppression after high dose prednisone therapy, espescially during induction to consolidation phase in ALL patients.

The aim of this study was to analyze of changes in cortisol level as marker of adrenal suppression which happened in children with standard risk acute lymphoblastic leukemia in induction and consolidation phase after high dose prednisone therapy for long period.

MATERIALS AND METHODS

This was a longitudinal observational, prospective, non-randomized trial study involving children with ALL who received prednisone for 49 days during the induction phase. We collected and compared the laboratory result of cortisol level in children with ALL and received prednisone therapy during induction to consolidation phase. We also collected data from the patients' medical record during the study period. Samples were taken for several weeks in the course of ALL chemotheraphy 2013 Indonesian protocol at Pediatric Department, Dr. Soetomo Hospital, Surabaya. In this study, we did not change or intervene the che-motherapy protocol used in Haematology Oncology Division Pediatric Department of Dr. Soetomo Hospital, Surabaya.

Blood samples were collected from all patients diagnosed with ALL standard risk and received prednisone therapy dose of 40 mg/m2/day for 49 days. Blood samples were taken in week 0, 4, 5, 6, 7, 8, 10, and 12 in order to analyze cortisol level. The blood collected for measurement was centrifuged at rate 2000-3000 rpm for 20 minutes to get the serum. The samples were stored at -80ºC freezer. Serum cortisol concentration was measured by ADVIA Centaur® XP Immunoassay Systems Cortisol. We performed the analysis in Clinical Pathology Laboratory, Dr. Soetomo Hospital, Surabaya.

Descriptive analysis was performed to determine the demographic, patients' characteristics, and the profile of cortisol serum at weeks 0, 4, 5, 6, 7, 8, 10, 12. Changes cortisol level was measured by SPSS software using paired t-test methods. A p value <0.05 was regarded as significant.

RESULTS

There were 13 patients (8 males, 5 females) between June 2016 – January 2017. The demography and characteristic of the patients included in this study are shown in Table 1. Mostly patients' age (76.9%) was 1-5 years and the number of male patients (61.5%) was higher than female patients (38.5%). The morphology result of BMP showed 8 patients (61.5%) belonged to LLA-L1 and 5 patients (38.5%) belonged to LLA-L2.

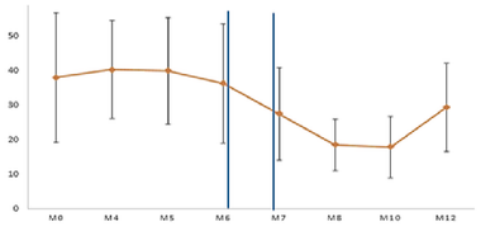

Fig. 1. Cortisol level profile in patient ALL standard risk.

Table 2. Average of cortisol level

Weeks	Cortisol levels
0	38.04 ± 18.82
4	40.28 ± 14.16
5	39.97 ± 15.41
6	36.27 ± 17.33
7	27.52 ± 13.33
8	18.55 ± 7.49
10	17.93 ± 8.89
12	29.32 ± 12.81

DISCUSSION

Acute Lymphoblastic Leukemia (ALL) is a group of lymphoid disorders produced by monoclonal prolife-

ration and expansion of immature lymphoid cells in the bone marrow, blood and other organs (Jabbour et al 2005, Lanzkowsky 2011). Other than that ALL is a malignancy mostly occur in children age 0-15 years (Ward et al 2014).

Glucocorticoid mechanism that is used in the treatment of ALL was to induce apoptosis of leukemia cells. The choice of glucocorticoid therapy used for standard risk LLA patients is prednisone. Prednisone has an important role in the induction phase of the treatment, but the supraphysiology dose of prednisone is expected to cause suppression in adrenal function and disturbance in the body response to stress and inadequacy of immune response to infection. Besides, adrenal suppression also causes acute insufficiency or chronic adrenal function (Shulman et al 2007).

High dose (>20 mg/m2/day) and long term (>30 day) prednisone therapy can cause a variety of side effects, especially HPA axis suppression. This can cause suppression of the synthesis of endogenous steroid cortisol by the suppression of the adrenal cortex (Longui 2007, Gupta & Bhatia 2008, Chrousos et al 2011). Reduced cortisol production causes adverse impacts, including insulin antagonist function, uncontrolled blood pressure, and impaired concentration of various enzymes involved in the metabolism. Other than that, cortisol also plays an important role in inflammation (anti-inflammatory) by blocking the production of leukotrienes, prostaglandins and lysosomal membrane stabilization, as well as immunosuppressive effects through suppressing the growth and function of immune cells, such as lymphocytes (Shulman et al 2007). Therefore, it is necessary and important to monitor the changes of cortisol levels as a parameter and other clinical parameters, such as blood pressure, blood sugar, nausea or vomiting, weakness or fatigue, acute dehydration, weight loss, abdominal pain, etc. (Hochberg et al 2003, Einaudi et al 2008).

Table 1. Patients' characteristics

Patients' characteristics		Patient total (N = 13)	
		N	%
Sex	Male	8	61.5
	Female	5	38.5
Age	1-5 years	10	76.9
	> 5 years	3	23.1
BMP morphology	L1	8	61.5
	L2	5	38.5
Haemoglobin (g/dL)	< 5.00	0	0
	5.00 – 6.90	1	7.7
	> 6.90	12	92.3
Leukocyte (g/dL)	< 5.000	6	46.1
	5.000 – 50.000	7	53.9
	> 50.000	0	0
Thrombocyte (g/dL)	< 50.000	8	61.5
	50.000-100.000	4	30.8
	> 100.000	1	7.7
Cortisol level at baseline (W0)	< 3 µg/dL	0	0
	3 – 21 µg/dL	2	15.38
	> 21 µg/dL	11	84.62
Total patients	W0 – W4	13	100
	W0 – W5	13	100
	W0 – W6	13	100
	W0 – W7	13	100
	W0 – W8	12	92.3
	W0 – W10	11	84.62
	W0 – W12	10	76.9
Clinical condition of patients before chemotherapy			
- Fever		4	30.8
- Cough		1	7.7
- Febril Neutropenia		4	30.8
- Pneumonia		1	7.7

Table 3. Patients' cortisol level

Px initial (Sex / Age)	Cortisol level (mcg/dL)							
	Week-0	Week-4	Week-5	Week-6	Week-7	Week-8	Week-10	Week-12
SA (M/6)	25.39	20.40	31.37	26.07	20.46	14.01	11.86	13.91
CS (M/7)	31.79	39.90	28.08	13.58	19.61	17.75	12.05	27.16
FS (M/2)	25.52	43.97	21.99	11.42	16.02	14.99	11.56	15.88
DA (F/8)	13.14	33.71	32.76	47.13	29.79	32.83	37.99	45.72
AN (M/3)	32.60	44.72	40.15	25.16	16.76	10.04	21.89	25.73
ZH (F/5)	22.87	61.90	68.77	50.55	57.73	25.16	21.50	28.65
SK (F/5)	44.52	35.42	48.82	49.53	30.29	26.77	24.45	56.16
NA (F/4)	44.91	45.56	43.10	21.88	20.02	10.44	4.37	25.96
TH (F/2)	14.54	50.19	56.45	56.95	49.35	20.51	15.19	30.77
AR (M/2)	54.51	63.26	62.25	63.60	24.43	17.36	15.43	23.24
MR (M/1)	64.08	26.67	18.40	48.26	19.35	24.00	-	-
AF (M/2)	75.00	15.81	29.67	21.34	16.06	8.76	20.89	-
NT (M/4)	45.69	42.18	37.87	36.03	37.94	-	-	-

Table 4. Analysis of changes in cortisol level

Variables		N	Mean ± SD	Statistical Analysis	p value*
W0 vs W6	W0	13	38.04 ± 18.82	Paired T test	0.810
	W6	13	36.27 ± 17.33		
W0 vs W7	W0	13	38.04 ± 18.82	Paired T test	0.192
	W7	13	27.52 ± 13.33	Wilcoxon	0.221
W0 vs W8	W0	13	38.04 ± 18.82	Paired T test	0.017
	W8	12	18.55 ± 7.49		
W0 vs W10	W0	13	38.04 ± 18.82	Paired T test	0.027
	W10	11	17.93 ± 8.89		
W0 vs W12	W0	13	38.04 ± 18.82	Paired T test	0.783
	W12	10	29.32 ± 12.81		
W7 vs W6	W7	13	39.97 ± 15.41	Paired T test	0.359
	W6	13	36.27 ± 17.33		
W5 vs W7	W5	13	39.97 ± 15.41	Paired T test	0.001
	W7	13	27.52 ± 13.33	Wilcoxon	0.003
W7 vs W8	W7	13	39.97 ± 15.41	Paired T test	0.001
	W8	12	18.55 ± 7.49		
W7 vs W10	W7	13	39.97 ± 15.41	Paired T test	0.001
	W10	11	17.93 ± 8.89		
W8 vs W12	W8	12	18.55 ± 7.49	Paired T test	0.005
	W12	10	29.32 ± 12.81		
W10 vs W12	W10	11	17.93 ± 8.89	Paired T test	0.003
	W12	10	29.32 ± 12.81		

High dose prednisone therapy for 29 days required gradual dose reduction (tapering off). The aim of dose tapering is to prevent any secondary adrenal insufficiency (Pulungan et al 2010). Prednisone has a role in modulating vascular response to maintain cardiac contractility, modulating vascular response to ß-adrenoceptor agonists and involved in the metabolism of glucose in the liver. When prednisone therapy is stopped without tapering off the dose, altered clinical symptoms may occur, such as hypotension and secondary adrenal insufficiency (tachycardia, decreased stroke volume, decreased peripheral vascular resistance) and hypoglycaemia (withdrawal syndrome) (Barthel et al 2015).

Reduction of cortisol levels resulting from adrenal suppression provides high incidence of febrile neutropenia in patients receiving prednisone therapy that will increase the incidence of infection and increasing antibiotic therapy cost. From a study, incidence of infection was experienced by 8% of patients with acute or chronic adrenal suppression (Einaudi et al 2008). Acute insufficiency is characterized by acute dehydration, hypotension, hypoglycemia, and impaired mental status, while the chronic

insufficiency is characterized by anorexia, nausea, vomiting, loss of appetite, weight loss and depression (Shulman et al 2007). In long term, adrenal suppression will inhibit growth in children (Ahmet et al 2011).

CONCLUSION

Long-term high-dose prednisone therapy in standard risk LLA patients did not cause adrenal suppression until the week 6 of induction phase, the effect of decreased cortisol levels begun at weeks 7 and then recovered with a percentage decrease of 28% (mean cortisol levels was 27.52 µg/dL), a nadir in the week 10 consolidation phase with a percentage decrease of 51% (mean cortisol levels 17.92 µg/dL). Increased cortisol levels occurred in week 12 with percentage of increase 64% (mean cortisol levels was 29.31 µg/dL). At week 8 and week 10 each, there was one patient who experienced adrenal suppression.

REFERENCES

Ahmet A, Kim H, Spier S (2011). Adrenal suppression: a practical guide to the screening and management of this under-recognized complication of inhaled corticosteroid therapy. Allergy, Asthma & Clinical Immunology 7, 1-12

Ansari S, et al (2014). Suppression of adrenal axis function after high-dose steroid therapy for childhood acute lympoblastic leukemia in Iran. International Journal of Contemporary Pediatrics 1, 164-167

Christensen MS, et al (2005). Treatment-related death in childhood acute lymphoblastic leukaemia in the Nordic Countries: 1992-2001. British Journal of Haematology, 50-58

Chrousos GP, Katzung BG, Trevor AJ (2014). Adrenocorticosteroids & adrenocortical antagonists in: Katzung basic & clinical pharmacology. 13th Eds. New York: McGraw-Hill Education.

Conter V, et al (2009). Long-term result of the Italian Association of Pediatric Hematology and Oncology (AIEOP) Studies 82, 87, 88, 91 and 95 for childhood acute lymphoblastic leukemia. Leukemia 24, 255-264

Einaudi S, Bertorello N, Masera N, Farinasso L, Barisone E, et al (2008). Adrenal axis function after high-dose steroid therapy for childhood acute lymphoblastic leukemia. Pediatric Blood Cancer 50, 537-41

Gupta P, Bhatia V (2008). Corticosteroid physiology and principles of therapy. Indian J Pediatr 75, 1039-1044

Hochberg Z, et al (2003). Endocrine withdrawal syndromes. Endocrine Reviews 24, 523-538

Jabbour EJ, Faderi S, Kantarjian HM (2005). Adult acute lymphoblastic leukemia symposium on oncology practice: hematological malignancies. Mayo Clin Proceeding 80, 1517-1527

Lanzkowski P (2011). Leukemias in manual of pediatric hematology and oncology. 5th ed. United Stated: Academic Press, p 518-525

Longui CA (2007). Glucocorticoid therapy: minimizing side effects. J Pediatr 83, S163-171

Pui C (2000). Acute lymphoblastic leukemia in children. Leukemia. Current Opinion in Oncology 12, 3-12

Pulungan A, et al (2010). Korteks adrenal dan gangguannya. Buku ajar endokrinologi anak. Jakarta, Badan Penerbit IDAI, p 251-293

Prucker C, et al (2009). Induction death and treatment-related mortality in first remission of children with acute lymphoblastic leukemia: a population-based analysis of The Austrian Berlin-Frankfurt-Munster study group. Leukemia. UK, Macmillan Publishers Ltd

Shulman D, Palmert M, Kemp S (2007). Adrenal insufficiency: still a cause of morbidity and death in childhood. Pediatrics 199, 484-94

Silverman LB, et al (2000). Result of dana-farber cancer institute consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1981-1995). Leukemia. UK, Macmillan Publishers Ltd

Ward E, et al (2014). Childhood and adolescent cancer statistics. A Cancer Journal for Clinicians 64, 83-103

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