Article type: Research article

Association between Cortisol and Infection Risk of Children with Acute Lymphoblastic Receiving Induction and Consolidation Chemotherapy in Dr. Soetomo General Hospital Surabaya

Tutwuri Handayani[1], I Dewa Gede Ugrasena[2], Mia Ratwita Andarsini[3]

[1]Researcher, Pediatric Resident, [2]Professor, Lecturer, Senior staff in Hematology-Oncology Division, [3]Lecturer, Senior staff, Head Division of Hematology-Oncology Faculty of Medicine, Airlangga University, Dr. Soetomo General Hospital, Surabaya, Indonesia

Abstract

Background: Mortality due to Infection associated therapy in acute lymphoblastic leukemia (ALL) children remains high, although therapeutic success and survival rate are substantially improving.

Methods: This study used a pre and post-test group design for children aged less than 18 years with ALL newly diagnosed and receiving chemotherapy in pediatric patient of Dr. Soetomo hospital Surabaya.

Results: The study involved 25 subjects, 10 subjects were male, average age ranged from 3 to 9 years. The high risk-ALL subjects were 15 (60%), hyperleukocytosis 4 (16%) subjects and 7 (28%) subjects with leukopenia. Statistical analysis showed a significant difference in decreasing cortisol levels in week-4 compared to week-0 ($p < 0.001$) and an increased in cortisol levels between week-12 compared to week-10. The incidence of infection during induction phase is higher than the consolidation phase (40vs15). The relationship between the mean cortisol levels and the incidence of infection in general showed a significant difference in the induction phase of week-0 ($p=0.029$), week-4 ($p=0.041$), and week-6 ($p=0.005$).

Conclusion: In the induction phase, there is an association between mean cortisol levels and the risk of infection, but there is no such association in the consolidation phase.

Keywords: *Cortisol, Infection, Chemotherapy, Mortality, ALL children.*

Introduction

Acute lymphoblastic leukemia (ALL) is a type of cancer that is found in most of the children's cancer cases[1]. Treatment success and survival rates in ALL children continuously improved over time. Despite advancements in therapeutic outcomes, however, treatment-related toxicity remains high (21.4%)[2]. The survival rate for ALL patients has increased since 1980. Patients diagnosed with ALL since 2005-2009 are estimated to have a 10-year survival rate of 88% -93%[3,4]. However, the mortality rate from cancer, as well as toxicity from side effects and infections associated with therapy, is still quite high[5,6]. According to the data obtained from the medical records of Dr. Soetomo hospital in June 2006-December 2010, it was found that 23.9% of child ALL patients died while completing induction phase chemotherapy.

Glucocorticoids have an important role in the therapy of ALL in children by inhibiting growth and inducing lymphoblast apoptosis[7,8,9]. Genomic and non-genomic effects will increase with increasing doses given. Glucocorticoid therapy is given during the induction phase at high doses (Prednisone 40-60mg / m2 / day or Dexamethasone 6mg / m2 / day). Long-term, high-dose administration of glucocorticoids can suppress the hypothalamus-pituitary-adrenal axis (HPA). Reduced cortisol levels in the body can reduce anti-inflammatory effects and increase pro-inflammatory cytokines, increasing infection risk. Adrenal suppression triggered by corticosteroid induction may be a major factor in this infection[10,11].

While studies on cortisol levels in Indonesia as a result of high-dose glucocorticoid therapy are still contradictory, few studies have related high-dose glucocorticoid administration to adrenal suppression, infection, and the time required for adrenal suppression to recover during the induction and consolidation phases. Based on these data, research was conducted in order to examine the relationship between cortisol levels and the incidence of standard and high-risk child ALL patients infection during the induction and consolidation phases, as well as to evaluate the effect of pediatric therapy management and outcome for ALL children in Dr. Soetomo hospital in Surabaya.

Materials and Methods

This research examines the time periods of the induction and consolidation phases in a prospective observational analytic study with a pre and post-test group design. The study population was new patients diagnosed as high-risk and standard -risk ALL who received chemotherapy from the induction phase to the consolidation phase. Meanwhile, the sample of the study were children with new high-risk and standard-risk ALL who were treated in the inpatient room of the Hematology at Pediatric ward of Dr. Soetomo hospital who received chemotherapy until the consolidation phase at the time of the study and met the inclusion criteria.

Furthermore, the results of blood tests (cortisol) were reported in ALL patients without intervention or treatment of the chemotherapy protocol used at SMF Children's Health Sciences, Dr. Soetomo Surabaya's Hematology Oncology Division. The patient's progress will be monitored while they are undergoing chemotherapy at Pediatric ward of Dr. Soetomo hospital in Surabaya.

Results and Discussion

A total of 39 pediatric patients diagnosed with ALL and receiving care at the IRJ Pediatric Hematology-Oncology Department of Pediatrics, Dr. Sutomo Surabaya from June 1, 2019 to August 31, 2019. There were 25 patients who met the eligibility criterion for this study, while the remaining patients were not considered due to exclusion and drop-out criteria. There were 8 patients who stopped taking their medications after being diagnosed with ALL, and 6 patients died during the observation phase.

Following the diagnosis of ALL, the patient's cortisol level was tested for the basic cortisol level at week-0 (W0) before the patient received prednisone or dexamethasone, which formed the basis for the patient's cortisol level. The patient's blood was drawn seven times, week-0 (W0), at week-4 (W4), week-6 (W6), week-7 (W7) induction phase chemotherapy and at week-8 (W8), week-10 (W10) and week-12 (W12) consolidation phase chemotherapy. Throughout the course of the report, the occurrence of infection was tracked and registered. The study results were analyzed using patient characteristics, cortisol level profiles, and the rate of infection during the observation period. Prednisone and dexamethasone are two corticosteroids used in ALL treatment[12].

Cortisol levels were measured three times during the induction phase: before prednisone or dexamethasone treatment was administered at week-0 (W0), at week-4 (W4), and at week-6 (W6). The results revealed a cross reaction with prednisone treatment, which patients regularly took at 07.00 in the morning, obscuring the significance of cortisol levels at the

time of review. Cortisol levels started to rise by 38% in the seventh week of healing. Adrenal suppression is described as a reduction in the patient's cortisol levels as a result of prednisone and dexamethasone exposure to the HPA axis, as shown by cortisol levels falling below the normal range of cortisol levels according to age.

Reduced cortisol levels in the body can reduce anti-inflammatory effects while activating pro-inflammatory cytokines, raising the risk of infection. Adrenal suppression caused by corticosteroid induction may be a factor in this infection[10,11]. According to Table 1, the prevalence of adrenal suppression was observed in four patients prior to undergoing chemotherapy, with the majority of cases occurring between weeks four and six of the induction period. There were no patients who suffered adrenal suppression during the consolidation process, but hypercortisol was observed in some patients.

Table 1. Incidence of induction and consolidation phase of induction and consolidation phase of adrenal suppression in ALL-HR and ALL-SR patients.

Cortisol level profile	Number of patients (%)						
	W0	W4	W6	W7	W8	W10	W12
∑ Suppression	5 (20)	13(52)	14 (56)	5 (20)	0 (0)	0 (0)	0 (0)
∑ Normal	16(64)	12(48)	10 (40)	15(60)	23(92)	2 (8)	19(76)
∑ Hyper	4 (16)	0 (0)	1 (4)	2 (8)	2(8)	4(16)	6 (24)
Percentage of suppression (%)	20	52	56	20	0	0	0

Many patients in the induction process were found to have infections during the follow-up time. The percentage of high-risk ALL patients who get infected is higher than the number of standard-risk ALL patients. Fever, conjunctivitis, parotitis, mucositis, acute otitis media, measles, diarrhea, bacterial exanthema, abscess cellulitis, candidiasis, urinary tract infections, and sepsis are also possible clinical complaints. Positive cultures were obtained in four ALL patients, two of whom had Acinetobacter baumannii (+) culture results and two of whom had ESBL (+) E. coli culture results. There was no adrenal crisis syndrome in the patient during the observation period, which included frequent clinical testing and laboratory examinations for each point of chemotherapy.

This research found statistically and clinically significant variations in cortisol levels between patients with infection and those who did not during the induction period of week 0 ($p = 0.029$) and week 6 ($p = 0.031$). This is also supported by the fact that the trust index range is narrow. The data also revealed that there was no statistically relevant relationship between cortisol levels and the rate of infection at the week-4, week-7, and week-10 stages. The following tables provide a rationale for the preceding research:

Table 2. Statistical analysis of ALL-SR cortisol levels with the incidence of induction and consolidation phase infections

Data	Infection	n	Meana ± SD	p-valueb	CI 95%
Cortisol W-0	Yes	9	16,13 ± 3,85	0,029	10,76 (1,39-20,12)
	No	1	5,37 ± 0,0		
Cortisol W-4	Yes	4	8,92 ± 3,70	0,056	-5,43 (-11,09-0,24)
	No	6	14,35 ± 1,28		
Cortisol W-6	Yes	2	3,51 ± 2,16	0,031	-11,65((-21,95-(-1,34))
	No	8	15,16 ± 5,99		
Cortisol W-7	Yes	1	9,74 ± 0,0	0,428	-9,82 (-36,95-17,31)
	No	9	19,56 ± 11,16		
Cortisol W-8	Yes	0	-	-*	-*
	No	10	17,83 ± 8,21		
Cortisol W-10	Yes	1	12,55 ± 0,0	0,533	-4,38 (-19,88-11,13)
	No	9	16,93 ± 6,38		
Cortisol W-12	Yes	0	-	-	-
	No	10	22,40 ± 4,90		

a. Cortisol level (µg/dL).

b. Significant if $p < 0.05$ with paired t-test statistical test.

* The data cannot be analyzed because one of the variables with a value of 0.

The table below shows the outcomes of statistical analyses comparing ALL-HR cortisol levels to the rate of infection during the induction and consolidation processes. Except at the week-4 cortisol stage, the findings revealed that there was no substantial change in cortisol levels in patients with the occurrence of infection in ALL-HR during the induction and consolidation processes. The Mann-Whitney research study on the cortisol week-4 hypothesis test for the prevalence of infection reported p value = 0.009, indicating that there is a substantial differential between those who have an infection and those that do not.

Table 3. Statistical analysis of ALL-HR cortisol levels with the incidence of infection in the induction and consolidation phase

Data	Infection	n	Meana ± SD	p-valueb	CI 95%
Cortisol W-0	Yes	13	5,60 ± 5,97	0,991	0,05 (-9,42-9,52)
	No	2	5,55 ± 2,34		
Cortisol W-4	Yes	8	-	0,009c	-
	No	7	-		
Cortisol W-6	Yes	4	0,38 ± 0,51	0,226	-1,73 ((-4,68-,1,21))
	No	11	2,11 ± 2,65		

Cont... **Table 3. Statistical analysis of ALL-HR cortisol levels with the incidence of infection in the induction and consolidation phase**

Cortisol W-7	Yes	4	1,27 ± 2,18	0,224	-3,85 (-10,37-2,67)
	No	11	5,12 ± 5,77		
Cortisol W-8	Yes	3	6,55 ± 1,53	0,064	-4,62 (-9,57- 0,32)
	No	12	11,17 ± 3,80		
Cortisol W-10	Yes	3	11,59 ± 1,86	0,312	-2,26 (-6,88-2,37)
	No	12	13,84 ± 3,52		
Cortisol W-12	Yes	3	13,89 ± 2,03	0,425	-1,85 (-6,71- 3,01)
	No	12	15,74 ± 3,68		

a. Cortisol level (μg/dL)

b. Significant if $p < 0.05$ with paired t-test statistical test

c. Mann-Whitney test

During the induction process of chemotherapy, there were patients with adrenal repression, which was identified by cortisol levels that were lower than the range limit value for cortisol levels according to age. The amount of time it takes for the adrenal glands of each condition to return to natural cortisol levels following prednisone or dexamethasone treatment is different. ALL patients are given elevated doses of glucocorticoids for an extended period of time during chemotherapy. During the induction process, about half of the patients will be readmitted to the hospital due to febrile neutropenia or sepsis. If the HPA axis is suppressed at the moment, this will have a negative impact on the patient's health[13]. In this study there were 10 out of 11 patients (91%) who experienced an incidence of infection during the induction phase and 8 patients out of 10 (80%) during the consolidation phase (table 3).

In induction phase ALL chemotherapy, there was an increased incidence of mortality due to infection by 10% when prednisone therapy (40 mg/m^2/day) was replaced with dexamethasone (6 mg/m^2/day)[14]. Dexamethasone induces a sluggish and delayed rise in proinflammatory cytokine levels, resulting in an insufficient inflammatory response and a masking effect on the signs of infection that occur. Long-term dexamethasone treatment is accumulative and reduces the inflammatory reflex; additionally, it may induce an insufficient stress response and raise the likelihood of deadly infections[14].

Infection in high-risk ALL cases is not only the result of long-term utilization of high doses of dexamethasone, but may also be the result of the patient's disease path. The ALL patients have clinical symptoms such as anemia, thrombocytopenia, leukopenia/leukocytosis, and/or neutropenia as a result of bone marrow invasion. Infection in high-risk ALL cases is caused not only by long-term utilization of high doses of dexamethasone, but also by the patient's disease path. The ALL patients have clinical symptoms such as anemia, thrombocytopenia, leukopenia / leukocytosis, and/or neutropenia as a result of bone marrow invasion. Fever without a clear etiology is a manifestation of cytokine release or can be caused by neutropenia and immunosuppression[15].

In this study, four patients recovered from adrenal gland function at week eight, while the remaining

patients recovered normally at week ten. According to the findings of Salem et al., serum cortisol and ACTH levels returned to normal in the majority of ALL-HR patients around week 4 and around 2 weeks in ALL-SR patients. Serum DHEAS levels returned to normal in 45 percent of ALL-HR patients and 85-90 percent of LLA-SR patients two weeks before full adrenal recovery[16].

Conclusion

The following conclusion can be drawn from the analysis and discussion:

1. The decrease in children's cortisol levels during induction phase chemotherapy differs between ALL-SR and ALL-HR.

2. During the consolidation process of ALL-HR, there are differences in cortisol levels in ALL pediatric patients.

3. Infection occurs more frequently in pediatric ALL patients during the induction phase.

4. During the consolidation phase, the incidence of infection in pediatric ALL patients is lower.

5. During the induction phase, there is a relationship between the incidence of infection and cortisol levels in ALL children.

6. During the consolidation phase, there was no association between the incidence of infection and cortisol levels in ALL children.

Conflict of Interest: There was no report for potential conflicts of interest in this study.

Acknowledgment: We would like to thank our teacher Prof. Dr. dr. I Dewa Gede Ugrasena and Dr. dr. Mia Ratwita with their permission we were able to carry out this research properly. We also appreciate the help of nurses and residents who give the support and warm welcome to the authors.

Ethical Clearance: We obtained an approval of whole project from Ethical Committee Review Board of Dr. Soetomo General Hospital Surabaya. The Ethical Clearance has issued by the Clinical Research Unit of Dr. Soetomo General Hospital Surabaya, Indonesia number 1207/KEPK/2019.

Source of Funding: This study was funded by authors' private fund.

References

1. Imbach P. General Aspects of Childhood Leukemia. In: Imbach, P., T. Kühne and J. R. Arceci. (Eds.) *Pediatric Oncology: A Comprehensive Guide.* **3rd. Ed.** Switzerland: Springer International Publishing. 2014;1-20.
2. Loeffen EA, Knops RG, Feijen JB, Merks JH, Reedijk AM, Lieverst JA, et al. Treatment related mortality in children with cancer: prevalence and risk factors. *Europ J of Cancer*. 2019; **121**: 113-122.
3. Carroll WL, Bhojwan D, Min DJ, Raetz E, Relling M, Davies S, et al. Pediatric acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program.* 2003; 102-31.
4. O'Connor D, Bate J, Wade R, Clack R, Dhir S, Hough R, et al. Infection- related mortality in children with acute lymphoblastic leukemia: an analysis of infectious deaths on UKALL 2003. *Blood.* 2014; **124**: 1056-1061.
5. Lund B, Asberg A, Heyman M, Kanerva J, Harila-Saari A, Hasle H, et al. Risk factors for treatment related mortality in childhood acute lymphoblastic leukemia. *Pediatrik Blood and Cancer.* 2011; **56**: 551-559.
6. Goldbloom E, Ahmet A. Adrenal suppression: an under-recognized complication of a common therapy. *Paediatrics & Child Health.* 2010;**15**: 411-412.
7. Petersen KB, Muller J, Rasmussen M, Schmiegelow K. Impaired adrenal function after glucocorticoid therapy in children with acute lymphoblastic leukemia. *Med Pediatr Oncol*. 2003; **41**: 110-114.

8. Kuperman H, Odone-Filho V, Cristofani LM, De Almeida MT, Setian N, Damiani D. Evaluation of adrenal reserve in children with acute lymphocytic leukemia treated with prednisone or dexamethasone. *Horm Res Paediatr.* 2012; **78**: 73-80.
9. Pufall MA. Glucocorticoids and cancer. *Adv Exp Med Biol*. 2015; **872**: 315-333.
10. Inaba H, Pui CH. Glucocorticoid use in acute lymphoblastic leukemia: comparison of prednisone and dexamethasone. *The Lancet Oncology*. 2010; **11**: 1096-1106.
11. Buttgereit F, Da Silva JAP, Boers M, Burmester G-R, Cutolo M, Jacobs J, et al. Standadised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: currentqu ‘estions and tentative answers in rheumatology. *Ann Rheum Dis*. 2002; **61**: 718-722.
12. Schimmer BP. Funder JW. ACTH, Adrenal Steroid, and Pharmacology of the Adrenal Cortex. In: Brunton, L., B. Chabner and B. Knollman. (Eds.) *Goodman and Gilman’s The Pharmacological Basis of Therapeutics. 12th. (Ed)*. New York: McGraw-Hill Compagnies. 2011; **42**: 1209-1236.
13. Mahachoklertwattana P, Vilaiyuk S, Hongeng S, Okascharoen C. Suppression of adrenal function in children with acute lymphoblastic leukemia following induction therapy with corticosteroid and other cytotoxic agents. *J Pediatr*. 2004;**144**: 736-40.
14. Poele EM, Bont ES, Marike-Boezen H, Revesz T, Bökkerink JP, Bieshuizen A. Dexamethasone in the maintenance phase of acute lymphoblastic leukaemia treatment: is the risk of lethal infections too high?. *Eur J Cancer*. 2007; **43**(17):2532□6.
15. Hastings CA, Torkildson JC, Agrawal AK. Acute leukemias *in: Handbook of Pediatric Hematology and Oncology: Children’s Hospital and Research Center Oakland.* 2nd. Ed. America. John Wiley & Sons. 2012; **15**: 144-156.
16. Salem MA, Tantawy AA, El Sedfy HH, El Laboudy MA, Toaima DN, Mahmoud NH, Selim DM. A prospective study of the hypothalamic-pituitary-adrenal axis in children with acute lymphoblastic leukemia receiving chemotherapy. **Hematology**. 2015; **20**: 320-7.