



Transient diabetes mellitus secondary to l-asparaginase and dexamethasone during induction phase of acute lymphoblastic leukaemia therapy

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ABSTRACT

Diabetes mellitus (DM) is an unusual event following chemotherapy for acute lymphoblastic leukemia (ALL) and occurs in approximately 10 to 15% of pediatric patients with ALL. It has been attributed to the use of l-asparaginase, glucocorticoids, and to infection. Recent study revealed that children with ALL, who experienced hyperglycemia during induction therapy, demonstrates poorer relapse-free survival (RFS) and overall survival (OS) rates. Patients with hyperglycemia during treatment should be screened for clinical evidence of diabetes mellitus (DM), which may require more intensive supportive care than those without DM. Although DM is rare during treatment of ALL, it carries significant morbidity and mortality. We describe a case

of 13 years old Indonesian girl who was diagnosed with High risk ALL in January 2015. As part of the induction phase, she was treated with l-asparaginase 7500 u/m² for 3 weeks and oral dexamethasone 6 mg/m² for 6 weeks. Two weeks after l-asparaginase and four weeks of dexamethasone therapy, she had DM with blood serum glucose of 522 mg/dL, HbA1c was increased to 9.68% and C-peptide was 0.6 ng/mL. She was successfully treated with insulin therapy. Over the next 3 months, the blood glucose level was stable between 57 to 115 mg/dL. HbA1c was 5.1% and C-peptide was 3.20 ng/mL. Then, she was diagnosed with transient diabetes mellitus (DM).

Key words: *Acute lymphoblastic leukemia, diabetes mellitus, l-asparaginase, dexamethasone*

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ABSTRAK

Diabetes Melitus (DM) merupakan kondisi yang tidak lazim ditemukan pada pasien Leukemia Limfoblastik Akut (LLA) dengan kemoterapi. Insiden DM pada pasien anak dengan LLA adalah sebesar 10–15% dan berhubungan dengan pengobatan l-asparaginase dan glukokortikoid serta infeksi. Penelitian menunjukkan bahwa pasien LLA pada anak dengan DM selama kemoterapi fase induksi memberikan hasil *relapse-free survival rate* (RFS) dan *overall survival rate* (OS) yang lebih rendah. Kami melaporkan kasus pasien anak usia 13 tahun yang terdiagnosis LLA *high risk* fase induksi. Berdasarkan protokol kemoterapi, pasien mendapatkan regimen l-asparaginase 7500 u/m²

selama 3 minggu dan deksametason oral 6 mg/m² selama 6 minggu. Pada minggu kedua setelah pengobatan l-asparaginase dan empat minggu setelah deksametason, pasien mengalami DM dengan kadar glukosa serum 522 mg/dL, kadar HbA1c 9,68% dan C-peptida 0,6 ng/mL. Pasien memberikan respon yang baik dengan terapi insulin. Pada pemantauan selama 3 bulan, gula darah pasien menjadi stabil yaitu 57–115 mg/dL. Kadar HbA1c menurun menjadi 5,1% dan kadar C-peptida naik menjadi 3,20 ng/mL. Pasien di diagnosis sebagai *transient diabetes mellitus* (DM).

Kata kunci: *Leukemia limfoblastik akut, diabetes mellitus, l-asparaginase, deksametason*

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INTRODUCTION

The acute lymphoblastic leukemia (ALL) accounts for approximately 25% of all childhood cancers. Despite chemotherapy has significantly improved the event-free survival (EFS) and overall survival (OS), the recurrence and disease progression, as well as the drug toxicity -related mortality, are still

increasing.¹ The recent studies have found that during the child critical disease process, the incidence of hyperglycemia was one of the risk factors that would affect the prognosis, and the similar conclusion had been confirmed in the adult malignancies. The hyperglycemia might directly affect

the cell growth, and induce the drug resistance of tumor cells.²⁻⁵

The occurrence of hyperglycemia during the period of inductive remission chemotherapy is an independent risk towards the early recurrence and high mortality of ALL patients, compared to the non-hyperglycemic patients, the risks were 6.2 times, respectively. Recent study revealed that children with ALL, who experience hyperglycemia during induction therapy demonstrates poorer relapse-free survival (RFS) and Overall survival (OS) rates.^{6,7}

Studies explore that hyperglycemia has long been recognized as a consequence of l-asparaginase, corticosteroids (either prednisone or dexamethasone) as part of chemotherapeutic agents to ALL treatment. These medications are usually administered concurrently in high doses during the initial induction phase of chemotherapy. As a result, diabetes frequently develops during this phase, with resolution after the steroids and asparaginase have been discontinued or reduced in dose.⁸⁻¹⁰

Hyperglycemia occurs in approximately 10 to 15% of pediatric patients with ALL, associated with the use of l-asparaginase, glucocorticoids, infection, and the leukemic process itself.^{9,11,12} Currently, the report about impacts of hyperglycemia during the inductive chemotherapy towards the prognosis of child ALL is few, and the conclusions are inconsistent. We report a case of a 13 days old girl who developed diabetes mellitus following l-asparaginase and dexamethasone therapy as part of treatment for ALL.

Case Illustration

FJ, a 13 days old girl, was treated in pediatric hematology oncology department since december 2014 with the diagnosis of high risk acute lymphoblastic leukaemia (ALL). The patient was diagnosed ALL from bone marrow aspiration on December 24th 2014 and then received chemotherapy based on the Indonesian protocol acute lymphoblastic leukemia (ALL) 2013 high risk. Patient start receiving induction phase of chemotherapy on Januari 1st 2015 with regimens consisting of methotrexate intrathecal, vincristine 1.5 mg/m², oral dexamethasone 6 mg/m², daunorubicin 30 mg/m² and l-asparaginase 7.500 unit/m² three times a week for three weeks. The induction phase last for 6 weeks. On fourth week of induction phase (2 weeks after receiving l-asparaginase and 4 weeks of dexamethasone), she had hyperglycemia with sign of polyuria, polydipsi and polyphagia but without significant weight loss. She did not have a previous history of high blood glucose. The blood glucose was arranged between 75 to 90 mg/dL. She did not have a family history of diabetes mellitus or autoimmunity.

Patient was alert on physical examination. The pulse rate was 76/minute and regular respiratory rate was 20 times/minute, axillary temperature was 36.6°C. Her body weight was 30 kg, body height was 170 cm, mid upper arm circumference was 17 cm, her ideal weight was 54 kg and her standard mid upper arm circumference was 24.3 cm. Thus, according to the Waterlow criteria, her nutritional status was 55% (severe malnutrition).

The head was normocephali. The conjunctiva was anemic, the sclera was not icteric, and the pupil reflexes were normal. The ear nose and throat as well as neck examination were within normal limit. There was not any palpable lymph nodes nor nuchal rigidity.

The chest examination revealed no precordial bulging. Ictus cordis was palpable on the 5th intercostals space on the left midclavicular line. On auscultation, the first and second heart sounds were normal, without murmur. The movement of both sides of the chest was symmetrical. Vesicular respiratory sounds were noted, without wheezing or rales. The abdomen examination revealed no hepatomegaly and no splenomegaly. Bowel sound was normal and turgor was normal.

Tanner stage examination showed stage 2 with breast bud palpable and areola enlarge and from genital with minimal coarse of pubic hair, pigmentes hair mainly on labia.

Laboratory investigations showed capillary blood glucose high and serum blood glucose of 522 mg/dL. Arterial blood gas analysis showed a pH 7.39, bicarbonate 15.7 mmol/L, base excess -9.3 mmol/L. Due to recent chemotherapy, other parameters were also deranged, with a leukocyte count $1,18 \times 10^9/L$ (4.1 to $11.0 \times 10^9/L$) including significant netropaenia $0,611 \times 10^9/L$, haemoglobin count 9.87 g/dL (13.5 to 17.5 g/dL), and platelet count of $107 \times 10^9/L$ (140 to $440 \times 10^9/L$). Serum electrolyte found sodium 128 mmol/l, potassium 3,33 mmol/l, chloride: 79.7 mmol/l, calcium; 7.96 mmol/l. From urin analysis we found ketone +4, glucose +4.

Based on anamnesis and physical examination, the working diagnosis for the case was acute lymphoblastic leukemia (ALL) high risk with hyperglycemia and severe malnutrition. We planned for further laboratory test to diagnosed probably of diabetes mellitus condition of this patient. We found that the C-peptide was decreased at 0.6 ng/mL (0.9 to 7.1 ng/mL) and HbA1c was 9.68% (4 to 6%).

Based on the clinical manifestation and laboratory findings, the patient was then diagnosed with acute lymphoblastic leukemia (ALL) high risk induction phase fourth weeks and diabetes mellitus

and severe malnutrition. The medical management in this case was stabilize the blood glucose with a bolus regimen of insulin and postponed the chemotherapy until blood glucose under control. Dexamethasone also was ceased.

Over the next 3 weeks, the blood glucose of patient was stable. Her glycaemic control remained stable on insulin novorapid 14 units in the morning and 10 units in the evening with glucose level between 57 to 115 mg/dL and then she continued her protocol of chemotherapy until she completed induction phase with high dose dexamethasone and l-asparaginase.

Monitoring of blood glucose was done regularly and her blood glucose remained in stable state with insulin therapy. After four months, her C-peptide was increased to 3,20 ng/mL and HbA1c was decreased to 5.1%. The insulin was stopped. One month after insulin was stopped, the patient remains euglycaemic state. Then, the patient was diagnosed with transient diabetes mellitus.

DISCUSSION

Hyperglycemia occurs in approximately 10 to 15% of pediatric patients with ALL, associated with the use of l-asparaginase, glucocorticoids, infection, and the leukemic process itself.^{9,12} The risk and severity of hyperglycemia increase when l-asparaginase and glucocorticoids are used concomitantly, however it is generally self-limiting (temporary) resulting in no complications.⁸ Banihashem et al¹² showed that prevalence of transient hyperglycemia in pediatric patient with acute leukemia was 10.3%. The transient diabetes mellitus has been associated in about 1 to 14% of patient with hematologic malignancy treated with l-asparaginase.

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defect in insulin secretion, insulin action, or

both. Diagnostic criteria for diabetes are based on blood glucose measurements and the presence or absence of symptoms. Criteria for the diagnosis of diabetes mellitus are lists on the table 1.¹³

Hyperglycemia can be associated with some severe complications such as diabetic ketoacidosis (DKA). Despite the fact that hyperglycemia is commonly associated with l-asparaginase, DKA represents a rare condition with a reported prevalence of 0.8%.⁸ In the largest case series, DKA occurred in 6 out of 797 patient (incidence 7.5/1000).⁹ Mondal¹⁰ reported DKA in 2 children children receiving l-asparaginase for ALL.¹⁰ Alves et al¹⁴ described a case of DKA occurring in a 13 years-old girl treated with L-asparaginase and dexamethasone.

L-asparaginase hydrolyses l-asparagine to l-aspartic acid and ammonia. Asparagine is necessary for cell survival, and most normal cells have the enzyme l-asparagine synthetase, allowing synthesis of asparagine. Lymphoblasts in ALL lack l-asparagine synthetase, and therefore cannot survive asparagine depletion caused by l-asparaginase. The depletion of the systemic asparagine pool by l-asparaginase will then lead to cancer cell death. Administration of l-asparaginase as chemotherapy preferentially limits l-asparagine to leukaemic cells during the G1 phase of mitosis.¹⁵ l-asparaginase induces hyperglycemia via depletion of l-asparagine and as a consequence decrement of insulin synthesis, as pancreatic cells requires three l-asparagine molecules to generate each insulin molecule. Additionally, it decreases insulin secretion from pancreatic β -cells, impairs insulin receptor function, and causes hyperglycemia.^{9,15,16}

Glucocorticoids are important therapeutic agents for treatment of ALL and included in most pediatric ALL treatment protocols. Glucocorticoids have variety of effects that can cause hyperglycaemia or exacerbate pre-existing diabetes. The development of ketoacidosis in the setting of glucocorticoids is uncommon but has been previously described. The reported doses of prednisone ranged between 30 to 120 mg daily.¹⁵ Insulin was required transiently while the patient was receiving glucocorticoid therapy. Glucocorticoid contributes to the development of hyperglycemia by several mechanisms such as inhibiting glucose uptake in muscle, increasing hepatic gluconeogenesis, and exerting multiple effect on the receptor and post receptor activity of the beta cell in the pancreas. Glucocorticoid encourages breakdown of stored protein and fat which causes an increased stream of free fatty acids and branched amino acids to the liver. This increases hepatic glucose output. Hepatic glucose output is usually regulated by insulin, but the effect of insulin is diminished in the presence of steroids.

Table 1 Criteria for the diagnosis of diabetes mellitus¹³

1. Symptoms of diabetes plus casual plasma glucose concentration > 11.1 mmol/L (200 mg/dl)*
Casual defined as any time of day without regard to time since last meal
Or
2. Fasting plasma glucose > 7.0 mmol/l (> 126 mg/dl)
Fasting is defined as no caloric intake for at least 8 hour
Or
3. 2-hour postload glucose > 11.1 mmol/l (> 200 mg/dl) during an Oral Glucose Tolerance Test (OGTT)
The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved water or 1.75 g/kg of body weight to a maximum of 75 g

* Corresponding values (mmol/L) are > 10.0 for venous whole blood and > 11.1 for capillary whole blood and > 11.1 and > 6.3 for both venous and capillary whole blood

Glucose uptake by fat and muscle is reduced due to insulin resistance and direct steroid effects. Hence, it increases average glucose concentration by decreasing insulin sensitivity.^{17,18}

The combination of l-asparaginase and glucocorticoids, as well as the disease stress, might be the main reason of hyperglycemia. Zhang *et al*¹⁹ also suggested that leukemic process itself, through mechanisms as yet undetermined, could impair glucose metabolism appearing as the elevated level of basic glycosylated hemoglobin, insulin resistance or insulin receptor abnormalities.

In our case, patient had hyperglycemia on induction phase of chemotherapy, after being treated with l-asparaginase 7.500 unit/m² three times a week, two weeks after the last dose and oral dexamethasone 6mg/m² for fourth weeks. The C-peptide was decreased at 0.6 ng/mL (0.9 to 7.1 ng/mL) and HbA1c was 9.68% (4 to 6%). Previous history of blood sugar was within normal limit. Patient then was diagnosed with diabetes mellitus according to the clinical diagnostic of diabetes mellitus. It is possible that the combination of l-asparaginase and glucocorticoids represented synergistic factors for the development of diabetes mellitus in our patient.

The risk factors for predisposing of hyperglycemia in leukemic children treated with l-asparaginase are age above ten years, high-risk groups stratification, positive family history of diabetes mellitus, down syndrome, and obese.^{20,21} Zhang *et al*¹⁹ reported that the hyperglycemia incidence among the age ≥ 10 year old children was significantly higher than the lower age group (43.33% vs 19.23%, $P=0.008$). A number of studies had confirmed that the age >10 years old when initially diagnosed was the predilection age of hyperglycemia during the child ALL inductive remission period, and it was also a risk factor towards the ketoacidosis.²¹ Banihashem¹² reported that hyperglycemia patient (BMI > 95 centile) were more than twice as likely to have required insulin therapy compared to overweight patients and three times as likely to have required insulin compared to normal weight (BMI < 85 centile) patients. Our patient was 13 years old and was diagnosed with high-risk group. Therefore, according to the previous study, this patient had higher risk for develop hyperglycemia secondary to chemotherapy agents. The relationship between age above ten years and incidence of diabetes is best explained by the increase secretion of estrogen and testosterone during puberty, as both hormones have been shown to be associated with decrease glucose tolerance and hyperinsulinemia.

Chemotherapy today has significantly improved the prognosis of children with ALL. Although the event-free survival (EFS) and overall survival (OS)

have been significantly improved, the recurrence and disease progression, as well as the drug toxicity -related mortality, are still increasing.¹ The recent study suggested that the hyperglycemia occurrence during the inductive remission period was connected with the poor prognosis of child ALL, the cumulative 5 years relapse free survival rate and the overall survival rate of the hyperglycemia group were significantly lower than the euglycemia group. Several study also reported that hyperglycemia is associated with increased mortality in critically ill adult and pediatric patient without previous history of diabetes mellitus.^{8,20}

In addition to increased mortality rates, more infection has also been noted in patient who experienced hyperglycemia during illness.²⁰ Hyperglycemia may play role on immune function and inflammation, which may delay and decrease the intensity of treatment and thus directly impact survival. On the other hand, even though overt hyperglycemia can be an independent predictor factor for survival in children with ALL during induction therapy, DKA generally results in short term morbidity and hospital admission, without the alteration of ALL outcome and modification in the chemotherapeutic regimens. Fortunately, our patient achieved complete resolution of symptoms, normalization of laboratory results, without major adverse events regarding both diseases. During therapy with l-asparaginase, we recommend a close monitoring for hyperglycemia as well as ketoacidosis in order to reduce the adverse events related to both conditions.^{15,20}

Since hyperglycemia cannot be avoided in a certain proportion of patients given l-asparaginase and glucocorticoid for remission induction, we recommend close monitoring for glucosuria in patients with the risk factors identified in this study, particularly during the first week after l-asparaginase therapy. Whether changing the schedule of drug administration would reduce the frequency of hyperglycemia without affecting the remission induction rate remains to be determined.²¹

CONCLUSION

Hyperglycemia may occur of 10 to 15% of cases receiving l-asparaginase and glucocorticoids as part of the cornerstone treatment for ALL, which may present as mild glucose intolerance to severe hyperglycemia. Regular monitoring of blood sugar and periodic screening for diabetes mellitus is required particularly in these patients. Although Diabetes mellitus is rare during treatment with ALL, it carries significant morbidity and mortality. Furthermore, as these patients are treated in an out-patient setting, monitoring of blood glucose

should be encouraged during the use of these agents, with blood ketone levels checked if hyperglycaemia develops.

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