

# The Outcome of Children With Acute Lymphoblastic Leukemia Without Receiving Sufficient Dose of L-Asparaginase

Gholamreza Bahoush<sup>1</sup>, Leila Asgarzadeh<sup>1</sup>, Marzieh Nojomi<sup>2,3</sup>

<sup>1</sup> Department of Pediatrics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

<sup>2</sup> Preventive Medicine and Public Health Research Center, Psychosocial Health Research Institute, Iran University of Medical Sciences, Tehran, Iran

<sup>3</sup> Department of Community and Family Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

Received: 14 Nov. 2019; Accepted: 28 Feb. 2020

**Abstract-** In acute lymphoblastic leukemia (ALL) patients treated with L-asparaginase, discontinuation of the drug occasionally occur due to severe drug complications or resistance, however, due to the high efficacy of this drug in the recovery of patients and the prevention of disease recurrence, resuming the drug regimen is preferred in most patients. What we did in this study was to evaluate and compare the effects of clinical outcomes in the two modes of continuing and discontinuing drug use. In this retrospective cohort study, all children with ALL who had been treated with L-asparaginase during the years 2005 to 2015 were included in the study and categorized into two groups receiving complete treatment regimen (n=160) and those who had to discontinue the drug due to appearing complications (n=9). The rate of relapse and mortality rate was determined and compared across the two groups with a median follow-up time of more than 5 years. 5-yrs Overall survival of all enrolled patients in the groups continued and discontinued was 91.4±2.5% and 71.4±17.1%, respectively ( $P=0.792$ ). Also, 5-yrs event-free survival of the two groups was 75.8±3.5% and 71.4±17.1%, respectively ( $P=0.557$ ). Relapse was revealed in 17.5% and 33.3% respectively and mortality in 16.9% and 0.0% ( $P=0.261$ ). However, the overall prevalence of hypersensitivity reaction to the drug was significantly higher in those patients who discontinued their drug regimen (100% versus 24.4%,  $P<0.001$ ). Hypersensitivity reaction to drugs may be an important factor in discontinuing L-asparaginase in patients with ALL. The discontinuation of L-asparaginase supplementation due to various complications such as hypersensitivity reactions may be effective in the survival of these patients. However, accurate determination of the effect of discontinuation of this drug on the outcome of children with ALL requires a more comprehensive study with more complicated cases.

© 2020 Tehran University of Medical Sciences. All rights reserved.

*Acta Med Iran* 2020;58(3):109-114.

**Keywords:** Children; Acute lymphoblastic leukemia; L-asparaginase

## Introduction

Acute lymphoblastic leukemia (ALL) is a hematological malignancy caused by uncontrolled production of leukocytes and is identified as the most common malignancy in children, accounting for 25-30% of all malignancies in this age group. Significant improvement has occurred in the treatment of ALL in recent years. The long-term survival rate of patients has been upgraded to 80% (1,2). Despite success in the treatment of ALL, over 20% of patients still have the failure to treat the disease. In addition, treated patients occasionally show high levels of treatment-induced toxicity that need to change the therapeutic strategy (3).

Major drugs used in the phase of treatment include glucocorticoids, anthracyclines, vincristine, and L-asparaginase, which are used for long-term treatment in these patients (4,5). Asparaginases are enzymes derived from bacteria, and in this regard, three types of these enzymes are derived from *E. Coli* (6,7). In recent years, a significant improvement in ALL treatment has been obtained following the use of L-asparaginase and is therefore considered as the primary protocol for treating patients (8,9), however, determining severe side effects due to the toxicity of this drug is necessary for optimizing the dose of the drug and approaching the most appropriate therapeutic protocol. The use of a high dose of L-asparaginase and long-term use of it to reduce relapses

**Corresponding Author:** L. Asgarzadeh

Department of Pediatrics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran  
Tel: +98 9127929877, Fax: +98 2122220063, E-mail address: dr.l.asgarzadeh@gmail.com

## Outcome of insufficient dose of L-asparaginase

and to achieve complete recovery of treatment is sometimes necessary (10). In addition, the combined formula of L-asparaginase with steroids and other chemotherapy drugs such as methotrexate, vincristine, and mercaptopurine can double the effectiveness of L-asparaginase and bring about a better outcome for patients (11,12). Despite the successful role of L-asparaginase in the treatment of ALL children, its use is limited in this age range due to complications as well as drug toxicity.

Another important point when using L-asparaginase is the development of resistance patterns to L-asparaginase, which is mainly the result of producing antibodies in response to this drug. Repeated administration of L-asparaginase doses has led to an increase in the production of various antibodies and, therefore, has resulted in more hypersensitivity reactions (13,14). Additionally, some patients have to discontinue drugs because of potential adverse drug reactions, and especially allergic reactions, which is another challenge in treating these patients. Since the ultimate objective of the various chemotherapy regimens is to increase the survival rate of these patients, the question of which medication discontinuation will affect the outcome of these patients is a subject that needs further studies. Therefore, we decided to study the outcome of discontinuation of L-asparaginase in children with ALL in the past 10 years.

## Materials and Methods

In this retrospective cohort study, all children with ALL who had been treated with L-asparaginase during the years 2005 to 2015 were included in the study and categorized into two groups receiving complete treatment regimen ( $n=160$ ) and those who had to discontinue the drug due to appearing complications ( $n=9$ ). Since in each group, two bone marrow samples were taken 29 days after starting treatment as well as immediately after discontinuation of treatment, the success or treatment response or failure were also determined. Overall, patients were followed up routinely after discontinuation of treatment. During this period, the following patients were assessed for the probability of disease recurrence: 1) undergoing biopsy of the testes due to painless swelling of the testis, 2) palsy undergoing lumbar puncture referred with the symptoms of increased CSF pressure or cerebral, 3) undergoing bone marrow aspiration due to the appearance of fever, bone pain, bleeding, petechiae and purpura, lymphadenopathy, splenomegaly, or blast in peripheral blood. In the final, the rate of relapse and

mortality rate were determined and compared across the two groups continued the treatment and those who discontinued the consumption of drugs.

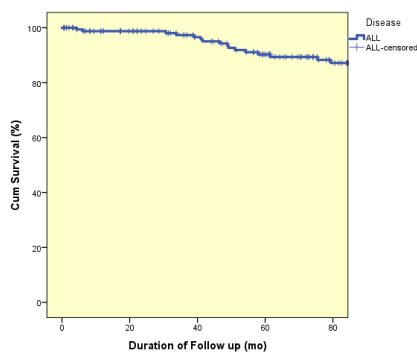
The results for the quantitative variables were expressed as mean and standard deviation ( $\text{mean}\pm\text{SD}$ ) and as number (percentage) for the qualitative variables. The t-test or Mann-Whitney U test was used to compare the quantitative variables. The Chi-square test also made a comparison between qualitative variables. To determine the event-free and overall survival of the patients within 5 years of follow-up, the Kaplan-Mayer analysis was employed. SPSS-23 software was used to analyze the data. The  $P$  of less than 0.05 was considered as significant.

## Results

Overall, 169 patients were initially assessed that 9 (5.3%) had to discontinue the treatment protocol with L-asparaginase. Compared the two groups with regard to baseline variables including gender, mean age, and laboratory baseline parameters (Table 1) showed that the patients discontinued the drug were older than other patients while gender distribution, mean hemoglobin level, the mean number of platelet and WBC counts were similar in the two groups. The median follows up of all enrolled patients in the two groups was 75.40 and 62.93 months, respectively ( $P=0.985$ ). Within this time, the rate of relapse was revealed in 17.5% and 33.3%, respectively, and mortality in 16.9% and 0.0% revealing a difference across the two groups in terms of treatment outcome, but they were not statistically significant ( $P=0.261$ ). However, the overall prevalence of hypersensitivity reaction to the drug was significantly higher in those patients who discontinued their drug regimen (100% versus 24.4%,  $P<0.001$ ). In the two groups with and without hypersensitivity reaction, 58.3% and 59.5% were males, respectively, with no difference ( $P=0.889$ ). According to the survival analysis, the 5-yr overall survival (OS) of all enrolled patients was  $90.3\pm 2.6\%$  (Figure 1). The five-year OS in the groups continued and discontinued L-asparaginase regimen was also  $91.4\pm 2.5\%$  and  $71.4\pm 17.1\%$ , respectively ( $P=0.792$ , Table 2, and Figure 2). The 5-yr event-free survival (EFS) of all enrolled patients was  $75.5\pm 3.6\%$  (Figure 3). The five-year EFS in the groups continued, and discontinued L-asparaginase regimen was  $75.8\pm 3.5\%$  and  $71.4\pm 17.1\%$ , respectively ( $P=0.557$ , Table 2, and Figures 4).

**Table 1. Comparing baseline parameters in the two groups**

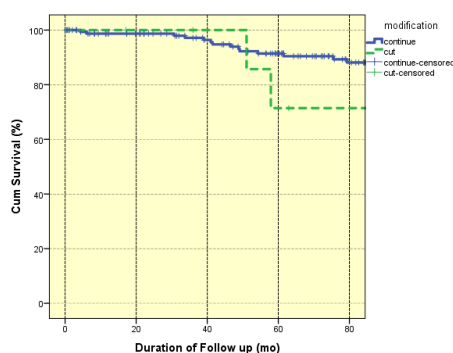
Parameter	Continuing drug	Discontinuing drug	P
<b>Gender</b>			0.999
Male	95 (59.4)	5 (55.6)	
Female	65 (40.6)	4 (44.4)	
Mean age	5.49 ± 3.50	8.04 ± 4.82	0.040
Mean hemoglobin	12.56 ± 4.39	9.43 ± 0.66	0.483
Mean platelet count	86294.77 ± 7612.89	122111.11 ± 42318.71	0.428
Mean WBC count	24764.15 ± 3275.18	22100.00 ± 11867.17	0.850
Median follow-up time (mo)	75.40	62.93	



**Figure 1.** Overall survival of all enrolled patients

**Table 2. 5-year survival in the two groups**

Parameter	Continuing drug	Discontinuing drug	P
<b>Free-even survival</b>			0.557
1- year	89.3%	100%	
2-year	86.7%	100%	
3-year	82.8	100%	
4-year	79.4	100%	
5-year	75.8	71.4%	
<b>Overall survival</b>			0.792
1- year	98.7%	100%	
2-year	98.7%	100%	
3-year	97.2%	100%	
4-year	93.0%	100%	
5-year	91.4%	71.4%	



**Figure 2.** Overall survival analysis of all enrolled patients with vs without asparaginase usage

## Outcome of insufficient dose of L-asparaginase

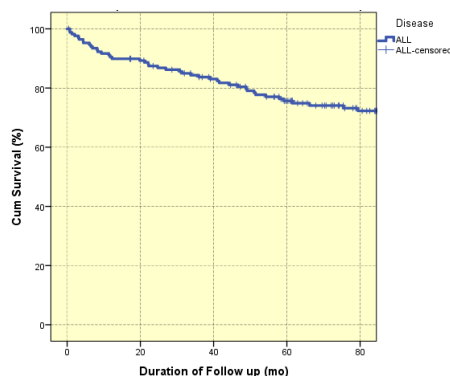


Figure 3. Event-free survival of all enrolled patients

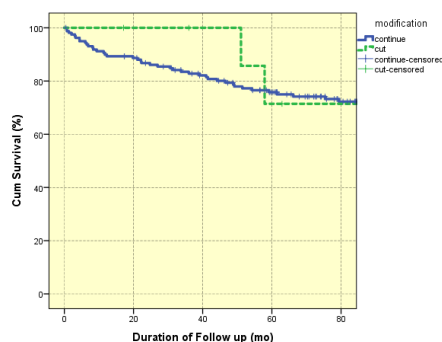


Figure 4. Event-free survival analysis of all enrolled patients with vs without asparaginase usage

## Discussion

In ALL patients treated with L-asparaginase, discontinuation of the drug occasionally occurs due to severe drug complications or resistance, however, due to the high efficacy of this drug in the recovery of patients and the prevention of disease recurrence, resuming the drug regimen is preferred in most patients. What we did in this study was to evaluate and compare the effects of clinical outcomes in the two modes of continuing and discontinuing drug use. What was considered as a consequence of the evaluation was the examination of recovery, recurrence, or mortality during follow-up in patients. In this study, patients in both groups were followed up for more than 5 years. Finally, in addition to studying mortality, relapse, and drug hypersensitivity, 5-year event-free survival and, as well as five-year overall, were compared between the two groups.

In summary, we found the following points. First, there was no statistical difference between the two groups with the continuation and discontinuation of the drug in the rate of improvement, the frequency of relapses, and the frequency of mortality; this may be due to the reduced number of cases in the second group. However, hypersensitivity reaction to drugs was significantly

higher in the group with discontinuation of the medication. Secondly, there was no difference between the two groups in evaluating the five-year survival of patients. As previously mentioned, although the use of high-dose and long-term use of L-asparaginase is necessary to reduce relapses and to achieve complete recovery of the treatment, its use at a young age is limited, and due to its complications, including drug toxicity, it is restricted. In particular, hypersensitivity reactions are one of the most common side effects of this drug as a major cause of drug discontinuation. In the present study, hypersensitivity reactions have been reported as an essential factor in the discontinuation of drug use. But more importantly, the continuation or discontinuation of L-Asparaginase similarly affects the long-term survival of patients. In other words, the pursuit of treatment regimens with and without continued administration of the drug leads to a long-term favorable outcome in patients. Of course, in our study, the number of patients in the drug discontinuation group was significantly lower, and this issue was considered as a limitation of the study. Therefore, the actual effect of L-asparaginase continuation on the long-term outcome of patients should be tested in later studies with a higher power.

In summary, what should be considered in this study

is firstly the introduction of hypersensitivity reactions as one of the most important factors in discontinuing the use of L-asparaginase in patients with ALL. As a second point, the discontinuation of L-asparaginase due to such a complication has not had a significant effect on the long-term survival of patients, probably because in both groups, it was a balance between the therapeutic efficacy of the drug and its complications. In a study by Usami *et al.*, first, the mean five-year event-free survival and overall survival of patients were estimated to be 94.4% and 97.5%, respectively, which was very close to the values obtained. But in their study, discontinuation of L-asparaginase drug was a predictor of poor prognosis and low survival (15). Of course, their study was first done on larger sample size, and secondly, a study was conducted on the Southeast Asian race, which could indicate a significant racial and genetic effect on the efficacy of the drug on the prognosis of patients, which, of course, needs to be studied more widely. In another study by Yen *et al.*, of the 700 patients enrolled in the study, 33 discontinued L-asparaginase treatment. The 5-year survival of patients with and without drug discontinuation did not differ (81% versus 88%) (16), which was consistent with our study. Also, in the study of Larson *et al.*, the three-year survival of patients receiving 14, 12 to 13, and lower than 11 doses of L-asparaginase were 55, 47, and 48 percent, respectively, with no significant difference (17), therefore, the outcomes of the disease were not dependent on the prescribed dosage of the drug, which could be consistent with our study.

Hypersensitivity reaction to drugs may be an important factor in discontinuing L-asparaginase in patients with ALL. The discontinuation of L-asparaginase supplementation due to various complications such as hypersensitivity reactions may be effective in the survival of these patients. However, accurate determination of the effect of discontinuation of this drug on the outcome of children with ALL requires a more comprehensive study with more complicated cases.

## Acknowledgements

The authors would like to thank Ali Asghar Clinical Research Development Center (AACRDC), for their support.

## References

1. Pinkel D. Curing children of leukemia. *Cancer* 1987;59:1683-91.
2. Pui CH, Sandlund JT, Pei D, Campana D, Rivera GK,

- Ribeiro RC, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIII B at St Jude Children's Research Hospital. *Blood* 2004;104:2690-6.
3. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. *New Engl j med* 2006;354:166-78.
4. Silverman LB, Gelber RD, Dalton VK, Asselin BL, Barr RD, Clavell LA, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. *Blood* 2001;97:1211-8.
5. Pieters R, Carroll WL. Biology and treatment of acute lymphoblastic leukemia. *Hematol Oncol Clin North Am* 2010;24:1-18.
6. Duval M, Suci S, Ferster A, Rialland X, Nelken B, Lutz P, et al. Comparison of Escherichia coli-asparaginase with Erwinia-asparaginase in the treatment of childhood lymphoid malignancies: results of a randomized European Organisation for Research and Treatment of Cancer-Children's Leukemia Group phase 3 trial. *Blood* 2002;99:2734-9.
7. Avramis VI, Tiwari PN. Asparaginase (native ASNase or pegylated ASNase) in the treatment of acute lymphoblastic leukemia. *Int j nanomedicine* 2006;1:241-54.
8. Ho DH, Whitecar JP, Jr., Luce JK, Frei E, 3rd. L-asparagine requirement and the effect of L-asparaginase on the normal and leukemic human bone marrow. *Cancer Res* 1970;30:466-72.
9. Pieters R, Hunger SP, Boos J, Rizzari C, Silverman L, Baruchel A, et al. L-asparaginase treatment in acute lymphoblastic leukemia: a focus on Erwinia asparaginase. *Cancer* 2011;117:238-49.
10. Amylon MD, Shuster J, Pullen J, Berard C, Link MP, Wharam M, et al. Intensive high-dose asparaginase consolidation improves survival for pediatric patients with T cell acute lymphoblastic leukemia and advanced stage lymphoblastic lymphoma: a Pediatric Oncology Group study. *Leukemia* 1999;13:335-42.
11. Asselin BL, Kreissman S, Coppola DJ, Bernal SD, Leavitt PR, Gelber RD, et al. Prognostic significance of early response to a single dose of asparaginase in childhood acute lymphoblastic leukemia. *J pediatr hematol oncol* 1999;21:6-12.
12. Abshire TC, Pollock BH, Billett AL, Bradley P, Buchanan GR. Weekly polyethylene glycol conjugated L-asparaginase compared with biweekly dosing produces superior induction remission rates in childhood relapsed acute lymphoblastic leukemia: a Pediatric Oncology Group Study. *Blood* 2000;96:1709-15.
13. Cheung NK, Chau IY, Coccia PF. Antibody response to Escherichia coli L-asparaginase. Prognostic significance and clinical utility of antibody measurement. *Am j pediatr*

## Outcome of insufficient dose of L-asparaginase

- hematol oncol 1986;8:99-104.
14. Woo MH, Hak LJ, Storm MC, Evans WE, Sandlund JT, Rivera GK, et al. Anti-asparaginase antibodies following E. coli asparaginase therapy in pediatric acute lymphoblastic leukemia. *Leukemia* 1998;12:1527-33.
  15. Usami I, Imamura T, Takahashi Y, Suenobu SI, Hasegawa D, Hashii Y, et al. Discontinuation of L-asparaginase and poor response to prednisolone are associated with poor outcome of ETV6-RUNX1-positive pediatric B-cell precursor acute lymphoblastic leukemia. *Int j hematol* 2019;109:477-82.
  16. Yen HJ, Chang WH, Liu HC, Yeh TC, Hung GY, Wu KH, et al. Outcomes Following Discontinuation of E. coli L-Asparaginase Upon Severe Allergic Reactions in Children With Acute Lymphoblastic Leukemia. *Pediatr blood cancer* 2016;63:665-70.
  17. Larson RA, Fretzin MH, Dodge RK, Schiffer CA. Hypersensitivity reactions to L-asparaginase do not impact on the remission duration of adults with acute lymphoblastic leukemia. *Leukemia* 1998;12:660-5.