

A Desensitization Protocol in Children With L-Asparaginase Hypersensitivity

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Background: L-asparaginase is effective in the treatment of malignant diseases, but it has been associated with hypersensitivity reactions in 5% to 45% of the patients.

Purpose: To determine whether a desensitization protocol in children with native *Escherichia coli* L-asparaginase hypersensitivity allows subsequent safe administration of native *E. coli* L-asparaginase.

Patients and Methods: A desensitization protocol was used in 9 children with leukemia (n = 8) or Langerhans cell histiocytosis (n = 1) and previous severe (n = 4) or mild/moderate (n = 5) L-asparaginase hypersensitivity. Dexamethasone (2 mg/kg intravenously) and pheniramine hydrogen maleate (1 mg/kg intravenously) were administered 1 hour before each of the following L-asparaginase administrations. Subsequently, 0.1%, 1%, 5%, 10%, and the remaining 84% of the total dose of L-asparaginase (10,000 IU/m²) were each prepared in 240 mL 0.9% saline and infused over 4 hours (20 h in total).

Results: After desensitization, none of the patients had recurrence of hypersensitivity reactions during the subsequent 2 to 15 doses (median: 6 doses/patient; 68 doses in total) of native *E. coli* L-asparaginase.

Conclusion: This desensitization protocol was safe and allows continued administration of native *E. coli* L-asparaginase administration.

Key Words: asparaginase, hypersensitivity, desensitization

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L-asparaginase is a cancer chemotherapeutic agent derived from *Escherichia coli*. It is effective in the treatment of acute lymphoblastic leukemia (ALL) and some other malignant diseases, but it has been associated with hypersensitivity reactions in 5% to 45% patients studied.^{1–5} These reactions can occur after 1 dose of the drug, but most occur after 2 weeks of daily or thrice weekly therapy.⁶ The risk factors for allergic reactions observed when L-asparaginase was given as a single agent or when given in higher doses (6000 IU/m²).⁶ Mechanisms proposed for L-asparaginase reactions include traces of endotoxin contamination, IgE-mediated hypersensitivity, IgG or IgM antibody-mediated sensitivity, and complement-mediated reactions.⁷ In case of hypersensitivity reactions, discontin-

uation of L-asparaginase and substitution with Erwinia or polyethylene glycol (PEG)-asparaginase is preferred.^{8,9} In many parts of the world, PEG asparaginase and Erwinia asparaginase availability is limited, and thus premedication protocols, desensitization protocols, or both might be an alternative practice. Some attempts to develop desensitization protocols for *E. coli* asparaginase have been reported in previous studies, but this aspect was not discussed in detail or the protocols were not studied in large numbers of patients.^{10–12} Bonno et al¹² successfully used desensitization protocol in 2 patients with anaphylaxis against to L-asparaginase. In our study, a similar desensitization protocol was applied to 9 children with L-asparaginase hypersensitivity. The aim of this study was to determine safety of a desensitization protocol in children with systemic hypersensitivity reactions to L-asparaginase.

MATERIALS AND METHODS

The study includes 9 patients with systemic hypersensitivity reactions to L-asparaginase (Leunase; Kyowa Hakko Kogyo Co, Tokyo, Japan) who were followed owing to oncologic or hematologic disease at Department of Pediatric Hematology, Faculty of Medicine, Yüzüncü Yıl University, between February 2007 and July 2009. L-asparaginase was used in a total of 40 patients with malignancy of whom 9 developed L-asparaginase hypersensitivity during the study period. The patients did not receive any other concomitant medications at the time of asparaginase allergy development. No other side effects of asparaginase (eg, pancreatitis, thrombosis/bleeding, etc) except for allergy were noted in the patients.

As the definition of anaphylaxis staging the following criteria was used; it was accepted mild-to-moderate anaphylaxis, if skin findings are accompanied by a history of shortness of breath or dyspnea, wheeze, hoarseness, nausea or vomiting, neurologic or cardiovascular features, normal heart rate, blood pressure, and Glasgow Coma Scale. A patient with potentially life-threatening symptoms or signs in conjunction with any of the findings listed for mild-to-moderate anaphylaxis is accepted as severe anaphylaxis. Severe symptoms include anyone or more of the following: history of loss of consciousness, syncope or lightheadedness at any time, systolic blood pressure of < 90 mm Hg, Glasgow Coma Scale score of < 15 because of hypoxia, hypoperfusion and direct effect of mediators, stridor, cyanosis, laryngeal edema, or a respiratory rate of 25 breaths/min or greater because of respiratory system dysfunction.⁵

In Turkey, only L-asparaginase is available, Erwinia and PEG asparaginase could not be easily obtained. Commercial supply of L-asparaginase was used in all patients. If the child

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experienced a systemic allergic reaction to L-asparaginase, either an acute allergic reaction or anaphylaxis, we recommended Erwinia or PEG asparaginase (Oncaspar; Rhonr-Pooulene Rorer, Collegeville, PA), which were exported. If Erwinia or PEG asparaginase could not be provided by parents, premedication and desensitization protocol for L-asparaginase was administered.

The local ethical committee of our hospital approved the study. An approval agreement form was received from the committee.

Investigated Parameters

In all patients, age, sex, personal and family history for atopic/allergic diseases, concomitant drug hypersensitivities, clinical symptoms/signs, and eosinophilia were noted. Eosinophil count was carried out immediately after the allergic reaction. In addition, allergic reactions or other complications were noted during desensitization.

Used Treatment Protocols

According to H-9926-LCH III protocol, patients receive 30 doses of L-asparaginase (10,000 IU/m² intravenously) once a week for 30 weeks. In St Jude Total XIII protocol, patients receive 25 doses of L-asparaginase (10,000 IU/m² intravenously) 9 doses each (3 times a week) in the induction and reinduction phases and 7 doses (once a month) in the maintenance phase. In BFM protocol, children receive 12 doses of L-asparaginase; 8 doses (5000 IU/m² intravenously) every 3 days in the induction phase and 4 doses (10,000 IU/m² intravenously) every 3 days in the reinduction phase. In BFM-2000 relapse protocol, L-asparaginase (10,000 IU/m² intravenously) is given in 7 doses. No premedications such as steroids and/or antihistamines were used before each asparaginase dose. The durations of asparaginase infusion in the 4 treatment protocols were 1 hour.

Preparation of Premedication and Desensitization Protocol

A single dose of dexamethasone (2 mg/kg intravenously, maximum 16 mg) and pheniramine hydrogen maleate (1 mg/kg intravenously, maximum 40 mg) was administered 1 hour before each of L-asparaginase infusion for premedication. For desensitization, L-asparaginase was given to patients for a longer period (16 h). Firstly, 0.1% of the total dose (10,000 IU/m²) was prepared in 240 mL 0.9% saline solution and infused in a titration of 60 mL/h. Secondly, 1% of the total dose and then 10% of total dose were given to patients. These doses were prepared in the same amount and type of the fluid, which was used in first dose preparation and given in a titration of 60 mL/h. Finally, the remaining amount of the total dose was prepared and given in the same way as the administration of the first dose. In all patients, the desensitization was carried out on each of L-asparaginase administrations.

Statistical Analysis

Statistical analyses were performed using the SPSS 17.0 software package program. Mann-Whitney *U* test was used to compare the mean values of ages between the patients with and without L-asparaginase hypersensitivity and χ^2 test was used to compare the patients for sex. The results were expressed as mean $\pm$ SD. A *P* value of <0.05 was considered significant.

RESULTS

All of 40 patients except, 1 who had LCH, were diagnosed with acute lymphocytic leukemia. Of 40 patients, 9 patients developed L-asparaginase hypersensitivity. All of the patients with L-asparaginase hypersensitivity were males. The age of children varied from 2 to 17 years (8.2 ± 5.1 y). Of the 31 patients without L-asparaginase hypersensitivity, 20 (64.5%) were males, 11 (35.5%) were females. The mean age was 6.2 ± 2.9 years (0.9 and 12 y). When compared the groups with and without L-asparaginase hypersensitivity, there was a statistically significance difference between the groups for sex ($P < 0.05$), but there was no significant difference between the groups for age ($P > 0.05$).

Clinical and laboratory characteristics of the patients with L-asparaginase hypersensitivity is given in Table 1. No personal and family history for atopic disease was observed. One patient (case 9) had a history of vincristine-induced polyneuropathy. The mean eosinophil percentage was 1.5 ± 1.0 with the range from 1% to 4%. Severe and mild/moderate anaphylaxis were noted in 4 and 5 patients, respectively. The most observed symptoms/signs were urticaria, dyspnea, and cyanosis. Of the 9 children, 8 had ALL and 1 had LCH. One child with ALL (case 6), who was treated with BFM-2000 relapse protocol also had central nervous system involvement. Various treatment protocols were used in the patients. Follow-up data about allergic reaction and desensitization in detail is given in Table 1. None of the patients had recurrence of hypersensitivity reactions during the subsequent 2 to 15 doses (median: 6 doses/patient; 68 doses in total) of native *E. coli* asparaginase.

DISCUSSION

The L-asparaginase enzyme is present in many plants and animals, but not in humans. The molecule of L-asparaginase is characterized by high molecular weight and a complicated protein structure. Thus, L-asparaginase is highly immunogenic in treated patients, which results in a specific humoral response.¹³ Allergic reactions against L-asparaginase are significant side effects and can restrict the clinical use of the drug. Approximately 10% of all patients who are given L-asparaginase do not complete the planned course because of hypersensitivity, even when the preparation of the enzyme is changed to a different product.⁴ In our study, hypersensitivity reaction against L-asparaginase was determined in 9 (22.5%) of 40 patients who used L-asparaginase in our unit. This rate was consistent with the literature data in which the hypersensitivity reactions rate was mentioned between 5% and 45%.¹⁻⁵

Although the most common clinical manifestation of hypersensitivity is urticaria, the spectrum of allergic reactions ranges from localized erythema to systemic anaphylaxis. Other reported systemic hypersensitivity reactions include indurations, edema, swelling, chill, fever, tenderness, skin rashes, and respiratory system symptoms.^{5,9,14} In our study, all patients had urticaria and dyspnea. None of them died owing to anaphylaxis. In the literature, the number of fatal occurrences has been reported very low (ie, one in every 1000 patients who react), despite the relatively high incidence of anaphylactic reactions.¹⁵ In the study by Soyer et al,⁵ of the 19 patients 13 were males and 5 were females. In contrast, in our study,

TABLE 1. Clinical and Laboratory Characteristics of the Patient With L-Asparaginase Hypersensitivity

Case No.	Sex	Age (y)	Concomitant Drug Allergies	Eosinophil Count (/mm ³)	Anaphylaxis Type	Clinical Symptoms/Signs	Diagnosis	Treatment Protocol	Follow-up Data About Hypersensitive Reaction and Desensitization
1;	male	2	No	166	Severe	Urticaria, dyspnea, wheezing, cyanosis, drowsiness	Langerhans cell histiocytosis	H-9926-LCH III	An allergic reaction occurred while infusing the third dose. No allergic reaction occurred after starting the desensitization protocol for the following 13 doses
2;	male	9	No	28	Severe	Urticaria, dyspnea, stridor, cyanosis	Acute lymphoblastic leukemia	St Jude Total XIII	An allergic reaction occurred while infusing the first dose of reinduction. No allergic reaction occurred after starting the desensitization protocol for the rest 6 doses
3;	male	5	No	112	Mild/moderate	Urticaria, dyspnea	Acute lymphoblastic leukemia	BFM	An allergic reaction occurred while infusing the eighth dose. No allergic reaction occurred after starting the desensitization protocol for the rest 4 doses
4;	male	2	No	60	Severe	Urticaria, dyspnea, stridor, cyanosis	Acute lymphoblastic leukemia	St Jude Total XIII	An allergic reaction occurred while infusing the first dose of continue therapy. No allergic reaction occurred after starting the desensitization protocol for the rest 15 doses
5;	male	17	No	18	Severe	Urticaria, dyspnea, stridor, cyanosis	Acute lymphoblastic leukemia	St Jude Total XIII	An allergic reaction occurred while infusing the sixth dose of continue therapy. No allergic reaction occurred after starting the desensitization protocol for the following 5 doses
6;	male	11	No	161	Mild/moderate	Urticaria, dyspnea	Acute lymphoblastic leukemia (central nervous system relapse)	BFM-2000 relapse protocol	An allergic reaction occurred while infusing the first dose. No allergic reaction occurred after starting the desensitization protocol for the rest 6 doses
7;	male	10	No	66	Mild/moderate	Urticaria, dyspnea	Acute lymphoblastic leukemia	St Jude Total XIII	An allergic reaction occurred while infusing the fifth dose of continue therapy. No allergic reaction occurred after starting the desensitization protocol for the rest 2 doses
8;	male	5	No	77	Mild/moderate	Urticaria, dyspnea	Acute lymphoblastic leukemia	BFM	An allergic reaction occurred while infusing the eighth dose. No allergic reaction occurred after starting the desensitization protocol for the rest 4 doses
9;	male	13	Vincristine-induced polyneuropathy	55	Mild/moderate	Urticaria, dyspnea	Acute lymphoblastic leukemia	St Jude Total XIII	An allergic reaction occurred while infusing the third dose of continue therapy. No allergic reaction occurred after starting the desensitization protocol for the rest 13 doses

all patients with L-asparaginase hypersensitivity were males. When compared the patients with and without L-asparaginase hypersensitivity, we found a significant difference between the groups for sex ($P < 0.05$). This finding suggests that males were more prone to L-asparaginase allergy than females. However, male predominance may also be a coincidental.

The production of anti-asparaginase antibodies is common in children with ALL and has been found to be higher in children with clinical signs of hypersensitivity.¹⁶ It was established that the measurement of anti-asparaginase antibodies might play a role in predicting future hypersensitivity to the drug.¹⁶ The highly reactive nature of the L-asparaginase molecule is the result of its high molecular weight and complex quaternary structure, which lead to asparaginase-specific antibody formation.⁵ Woo et al² demonstrated that 30 of 54 antibody-positive patients experienced hypersensitivity reactions compared with 18 of 98 antibody-negative patients. As the level of asparaginase antibodies increased, the risk of a hypersensitivity reaction increased, but no correlation could be found between the severity of allergic reactions and antibody levels.² Unfortunately, in our study, anti-asparaginase antibody measurement could not be performed owing to lack of laboratory facilities.

The frequency and severity of allergic reactions depend on several factors such as the type of the enzyme, the route of drug administration, and the time point of treatment.¹⁶ L-asparaginase is administered by intramuscular or intravenous route. Intramuscular administration reduces the likelihood of severe allergic response. However, it is troublesome for patients with hemorrhagic diathesis, and up to 30% of children develop allergic reactions with intramuscular administration.¹⁷ Allergic reactions to one preparation can be circumvented by the substitution to another preparation. In the United States, L-asparaginase is the most commonly used preparation. Hypersensitivity reactions usually require discontinuation of L-asparaginase and substitution with the Erwinia or PEG asparaginase preparation.^{2,9,18} The properties of PEG asparaginase were intended to reduce the immunogenicity and the risk of hypersensitivity reactions and to prolong the half life of the drug.^{2,18} Thus, PEG asparaginase has been used in patients who have prior hypersensitivity to *E. coli* or Erwinia asparaginase.¹⁹ On the other hand, shortages of these alternative forms complicate the sufficiency of chemotherapy protocols in cases of hypersensitivity reactions, especially in developing parts of the world.⁵ In our study, Erwinia or PEG asparaginase preparation could not be obtained by the parents. Hence, the substitution process could not be performed and L-asparaginase was given by using desensitization protocol.

It is well known that one-third of the patients' hypersensitive to L-asparaginase were reported to experience allergic reactions to PEG asparaginase.²⁰ On the other hand, nearly, one-fifth of patients who had an allergic reaction to L-asparaginase had a subsequent allergic reaction to Erwinia-asparaginase in the form of mild urticaria.²¹ Conversely, Larson et al²² described 1 of 20 patient who was hypersensitive to L-asparaginase and later showed a reaction to Erwinia-asparaginase. In our study, none of the patients showed recurrence on hypersensitivity reaction after desensitization of L-asparaginase.

As in many regions of the world, in Turkey availability of PEG asparaginase and Erwinia asparaginase are limited,

and thus desensitization protocols, premedication protocols, or both might be an alternative way. Although, desensitization protocols for L-asparaginase hypersensitivity have been described, in the literature the sample size is too small to demonstrate any statistically significant assertion of the finding.¹⁴ In the study by Soyer et al,⁵ the first dose of L-asparaginase was given as 1 IU intravenously and was doubled every 10 minutes until the desired total dose was reached. In that study, 19 patients (13 male patients) with a mean age of 7.4 ± 4.7 years experienced a systemic hypersensitivity reaction to L-asparaginase during a 4-year period. PEG asparaginase could be used for 3 patients. Eight of the remaining 16 children, who had experienced anaphylaxis, were premedicated and desensitized with L-asparaginase, and in 7 patients treatment was tolerated. The other 8 patients, with acute allergic reactions to L-asparaginase were premedicated first, and 5 of them showed no reaction subsequently. Three of them demonstrated systemic hypersensitivity reactions again (anaphylaxis, $n = 3$), and premedication and desensitization with L-asparaginase resulted in anaphylaxis. PEG asparaginase was administered uneventfully to the patients who were able to obtain it. Finally, they suggested that in countries with shortages of alternative asparaginase preparations, their approach might be a suitable option. On the other hand, Bono et al¹² described another protocol in 2 patients with anaphylaxis against to L-asparaginase. In their protocol, 4 infusion bags that included 5, 50, 500, and 5000 IU L-asparaginase were prepared and each infusion bag was prepared in 250 mL 5% dextrose and dripped in about 4 hours. Our protocol was similar to the protocol of Bonno et al.¹² However, in our study, these 4 infusion bags included 0.1% of the total dose, 1%, 10%, and remaining of total dose, respectively. Each infusion duration was also in 4 hours in our study. No anaphylaxis or allergic reaction was noted.

In conclusion, we would like to emphasize that our premedication and desensitization protocol was safe and may be successfully used in developing countries like Turkey with shortages of alternative asparaginase preparations.

REFERENCES

1. Dellinger CT, Miale TD. Comparison of anaphylactic reactions to asparaginase derived from *Escherichia coli* and from *Erwinia* cultures. *Cancer*. 1976;38:1843-1846.
2. Woo MH, Hak LJ, Storm MC, et al. Anti-asparaginase antibodies following *E. coli* asparaginase therapy in pediatric acute lymphoblastic leukemia. *Leukemia*. 1998;12:1527-1533.
3. Cheung NK, Chau IY, Coccia PF. Antibody response to *Escherichia coli* L-asparaginase. Prognostic significance and clinical utility of antibody measurement. *Am J Pediatr Hematol Oncol*. 1986;8:99-104.
4. Müller HJ, Boos J. Use of L-asparaginase in childhood ALL. *Crit Rev Oncol Hematol*. 1998;28:97-113.
5. Soyer OU, Aytac S, Tuncer A, et al. Alternative algorithm for L-asparaginase allergy in children with acute lymphoblastic leukemia. *J Allergy Clin Immunol*. 2009;123:895-899.
6. Weiss RB, Bruno S. Hypersensitivity reactions to cancer chemotherapeutic agents. *Ann Intern Med*. 1981;94:66-72.
7. Fabry U, Korholz D, Jurgens H, et al. Anaphylaxis to L-asparaginase during treatment for acute lymphoblastic leukemia in children-evidence of a complement-mediated mechanism. *Pediatr Res*. 1985;19:400-408.
8. Hak LJ, Relling MV, Cheng C, et al. Asparaginase pharmacodynamics differ by formulation among children with newly diagnosed acute lymphoblastic leukemia. *Leukemia*. 2004;18:1072-1077.

9. Wang B, Relling MV, Storm MC, et al. Evaluation of immunologic crossreaction of antiasparaginase antibodies in acute lymphoblastic leukemia (ALL) and lymphoma patients. *Leukemia*. 2003;17:1583–1588.
10. Tallal L, Tan C, Oettgen H, et al. *E. Coli* L-asparaginase in the treatment of leukemia and solid tumors in 131 children. *Cancer*. 1970;25:306–320.
11. Clarkson B, Krakoff I, Burchenal J, et al. Clinical results of treatment with *E coli* L asparaginase in adults with leukemia, lymphoma, and solid tumors. *Cancer*. 1970;25:279–305.
12. Bonno M, Kawasaki H, Hori H, et al. Rapid desensitization for L-asparaginase hypersensitivity. *J Allergy Clin Immunol*. 1998;101:571–572.
13. Woo MH, Hak LJ, Storm MC, et al. Hypersensitivity or development of antibodies to asparaginase does not impact treatment outcome of childhood acute lymphoblastic leukemia. *J Clin Oncol*. 2000;18:1525–1532.
14. Narta UK, Kanwar SS, Azmi W. Pharmacological and clinical evaluation of L-asparaginase in the treatment of leukemia. *Crit Rev Oncol Hematol*. 2007;61:208–221.
15. Zubrod CG. The clinical toxicities of L-asparaginase in the treatment of leukemia and lymphoma. *Pediatrics*. 1970;45:555–559.
16. Zalewska-Szewczyk B, Andrzejewski W, Bodalski J. Development of anti-asparaginase antibodies in childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2004;43:600–602.
17. Nesbit N, Chard R, Evans A, et al. Evaluation of intramuscular versus intravenous administration of L-asparaginase in childhood leukemia. *Am J Pediatr Hematol Oncol*. 1979;1:9–13.
18. Evans WE, Tsiatis A, Rivera G, et al. Anaphylactoid reactions to *Escherichia coli* and Erwinia asparaginase in children with leukemia and lymphoma. *Cancer*. 1982;49:1378–1383.
19. Ettinger LJ, Kurtzberg J, Voute PA, et al. An open-label, multicenter study of polyethylene glycol-L-asparaginase for the treatment of acute lymphoblastic leukemia. *Cancer*. 1995;75:1176–1181.
20. Graham ML. Pegaspargase: a review of clinical studies. *Adv Drug Deliv Rev*. 2003;55:1293–1302.
21. Billett AL, Carls A, Gelber RD, et al. Allergic reactions to Erwinia asparaginase in children with acute lymphoblastic leukemia who had previous allergic reactions to *Escherichia coli* asparaginase. *Cancer*. 1992;70:201–206.
22. Larson RA, Fretzin MH, Dodge RK, et al. Hypersensitivity reactions to L-asparaginase do not impact on the remission duration of adults with acute lymphoblastic leukemia. *Leukemia*. 1998;12:660–665.