

L-ASPARGINASE INDUCED ANGIONEUROTIC EDEMA

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ABSTRACT

L-ASPase (L-asparaginase) is an important chemotherapeutic agent in the treatment of Acute lymphoblastic leukemia (ALL). Asparagine is required for the malignant growth of tumor cells especially lymphoblastic leukemia cells. An allergic response to L-ASPase is not unusual because it is derived from *Escherichia coli* and is often recognized as a foreign protein. The hypersensitivity induced by L-asparaginase is immediate type of hypersensitivity reaction. We report a 19 year old male with hypersensitivity reaction, angioneurotic edema (immediate type) developed after the second dose of L-asparaginase. He had not developed any adverse reaction in the first dose. He was

managed with corticosteroid and antihistaminics. The patient recovered and other chemotherapeutic drugs were continued for his present illness of B-cell ALL. This highlights the importance of giving test dose every time we use drugs known to cause hypersensitivity.

KEYWORDS: Acute Lymphoblastic Leukemia, hypersensitivity, angioneurotic edema.

CASE PRESENTATION

A 19 year old male who presented with fever of 2 weeks duration. On examination, he had pallor, splenomegaly and generalized lymphadenopathy (cervical, occipital, and inguinal). Laboratory results revealed that had anemia (hemoglobin-11.4g/dl), leucopenia (TLC-500cells/mm³) and thrombocytopenia (26,000 cells/mm³) and his peripheral blood smear showed 93% blast cells and immunophenotyping revealed that was positive for various B-cell lymphoid markers like CD19, CD10, CD20,CD38,CD79a,T-cell lymphoid markers-CD7(DIM) and precursor markers-Tdt, HLA-DR,CD 34. He was diagnosed to have B ALL – CALLA positive. His Liver function test and renal function test were within normal limits.

Patient was inducted into BFM 95 protocol and he was started on tablet wysolone, injection vincristine, injection daunorubicin, injection L-ASPase and intrathecal methotrexate. On the 12th day when L-asparaginase was given at the dose of 5000 international units/m² in 100ml normal saline for 15 minutes, he developed lip swelling and breathlessness within 5 minutes. The dose of L-ASPase was reduced on 12th day due to increase in the bilirubin levels. He also had hypotension (blood pressure 90/60), tachycardia and bronchospasm after the administration of the L-ASPase. No rash was detected and no delayed side effect was observed due to this drug. The drug was immediately stopped but patient had taken almost 75% of the drug. Antihistamines and steroid was given to counteract the hypersensitivity reaction. A diagnosis of angioneurotic edema due L-ASPase was made.

Lab Parameters

Before the adverse reaction of the patient to L-asparaginase the lab characteristics were as follows: hemoglobin-11.6g/dl, total leucocytes- 2600cells/mm³; platelets-41,000cells/mm³; urea-28 mg/l creatinine-0.4mg/l sodium-136mmol/l; potassium-4.1mmol/l ; total bilirubin-4.0mg/dl; direct bilirubin-1.6mg/dl, AST-16IU/L, ALT-34IU/L, ALP-63IU/L, total protein-5.6g/dl; albumin-3.6g/dl; globulin-2.0g/dl. Following reaction to the drug, there were not any significant laboratory value changes.

Treatment

The infusion was stopped immediately and patient was given one ampule of Avil (chlorpheniramine maleate) and injection Hydrocortisone 100mg i.v. The swelling around the lips subsided after 20 minutes but breathlessness subsided after four hours. No other active intervention was done and patient recovered completely on that day. The other chemotherapeutic drug was given in full dose. He was given platelet transfusion to treat thrombocytopenia.

DISCUSSION

Asparaginase hydrolyzes the amino acid L-asparagine to L-aspartic acid and ammonia. Asparagine is required for DNA synthesis and cell survival and most cells are capable of synthesizing asparagine from glutamine. In Acute lymphoblastic leukemia (ALL), cancer cells lack adequate levels of the required enzyme, asparagine synthetase, and cannot survive the asparagine depletion. Asparaginase is cycle-specific for the G1 phase.^[1] On the other hand, some malignant tumor cells show increased expression of asparagine synthetase through endoplasmic reticulum stress pathways or amino acid response pathways. An

increased expression of asparagine synthetase corresponds to decreased sensitivity to asparaginase.^[2] There are three formulations of asparaginase available, 1) Asparaginase (L-asparaginase isolated from *E.coli*) 2) Erwinia asparaginase (L-asparaginase isolated from *Erwinia chrysanthemi*) 3) Pegaspargase (L-asparaginase isolated from *E.coli* and attached to polyethylene glycol) Erwinia asparaginase is serologically and biochemically distinct from asparaginase but the antineoplastic activity and toxicity is similar. Pegaspargase has a longer half-life and decreased toxicity.^[1]

Patient's immune system recognizes L-ASPase as a foreign substance because it is a large enzyme (140 KD) and is derived from *E.coli*.^[3] During clinical trials, a significant hypersensitivity reaction has occurred with all three formulations. Reactions include rash, urticaria, edema, face swelling, hypotension, respiratory distress, chills, fever and anaphylaxis, which may result in sudden death. This can be correlated with our patient who developed respiratory distress and lip swelling. An intradermal test dose is recommended for asparaginase but not for Erwinia asparaginase or pegaspargase. This patient did not receive a test dose but he had tolerated the first dose of L-ASPase. It has the highest frequency of hypersensitivity reactions accounting for 15-35% of the total adverse reactions during clinical trials. Although skin testing is not completely reliable in predicting asparaginase hypersensitivity, an intradermal test dose is generally recommended prior to the first dose, or before restarting therapy after several days. Anaphylactic reactions can occur within one-half to one hour following the first injection and it occurs mainly between the fifth and ninth injection and the above patient showed reactions during the infusion of second injection. Risk factors of hypersensitivity are IV administration lower in IM or SC administration, prolonged therapy, high dose (> 6,000-12,000) international units/m², previous asparaginase therapy, and intermittent dosing. Up to 33% of patients who had an allergic reaction to asparaginase will also react to Erwinia asparaginase.^[1] The dose for B-cell ALL in most protocols ranged from 5000 to 10,000 IU/m given on multiple days and the above patient had L-asparaginase dose within the range.^[2]

With regard to hypersensitivity reactions, recent case report revealed that a 5 yr old girl diagnosed as T-cell lymphoblastic leukemia treated with Tokyo Children Cancer Study Group Protocol (includes L-ASPase drug) developed delayed type of hypersensitivity reactions in the form of blisters and erythema at the site of catheter insertion.^[3] Recent studies where 410 children were treated on St. Jude Total XV protocol for acute

lymphoblastic leukemia (which included L-asparaginase) had shown clinical allergy in 41% patients. Here 87% percent of the patients showed anti-asparaginase antibodies.^[4,5] This shows a correlation between the antibodies and hypersensitivity reaction. Examination of data from European ancestry patients enrolled into St. Jude Children's Research Hospital (n=5541) and the Children's Oncology Group (n=51329) clinical trials, identified a higher incidence of allergic reactions and anti-asparaginase antibodies in patients with HLA-DRB1*07:01 alleles.^[6] Studies have shown that genetic variations in GRIA1 on chromosome 5q33 was related to asparaginase hypersensitivity.^[7]

CONCLUSION

The author wants to conclude that L-ASPase does cause hypersensitivity reactions every time and it is always recommended to give intradermal test before giving the drug. In case of future hypersensitivity reactions, it is better to estimate anti-asparaginase antibodies because of its positive correlation.

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