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Case Report

An experience with plasma exchange treatment of acute lymphoblastic leukemia in a case with fulminant hepatitis related to L-asparaginase

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is a malignant disorder resulting from the clonal proliferation of lymphoid precursors with arrested maturation. L-asparaginase is commonly used in combination chemotherapy of both pediatric and adult acute lymphoblastic leukemias. The most commonly encountered side effects of L-asparaginase are hypersensitivity reactions like pyrexia, urticaria, skin rash, and respiratory distress. There are also other side effects like anaphylaxis, coagulopathy, pancreatitis, thrombosis, and hepatic toxicity. Plasmapheresis can sometimes be appropriate to manage an overdose of drugs that circulate in the plasma compartment.

We have reported plasmapheresis treatment of fulminant hepatitis in a patient with ALL after L-asparaginase treatment.

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1. Introduction

Acute lymphoblastic leukemia (ALL) is a malignant disorder resulting from the clonal proliferation of lymphoid precursors with arrested maturation. The disease can originate in lymphoid cells of different lineages, thus giving rise to B-cell or T-cell leukemias or sometimes to mixed lineage leukemia [1]. L-Asparaginase is commonly used in combination chemotherapy of both pediatric and adult acute lymphoblastic leukemias [2,3].

Frequent allergic reactions can be developed during L-asparaginase treatment, which is an important agent in ALL. The incidence of allergic reactions is reported to be 6–43% during intravenous L-asparaginase treatment. Therefore, L-asparaginase treatment is generally applied intramuscularly or subcutaneously. However, allergic reaction incidence is reported as 25% during weekly high

dose intramuscular L-asparaginase treatment. The most commonly encountered allergic reactions during L-asparaginase treatment are pyrexia, urticaria, skin rash, respiratory distress, hemolytic anemia, thrombocytopenia, interstitial nephritis, serum sickness, cutaneous eruptions and vasculitis [4]. Other L-asparaginase treatment related side effects may also be encountered like acute pancreatitis, coagulation disorders, immunosuppression, and hepatic injury [5]. Although L-asparaginase is an important agent in ALL treatment, its use is limited due to its side effects. Moreover, plasma concentration of L-asparaginase treatment is increased by its repetitive applications during the treatment [6].

Plasmapheresis can sometimes be appropriate to manage an overdose of drugs that circulate in the plasma compartment [7].

We have presented our case with ALL, which was at Hoelzer protocol phase 1, and developed fulminant hepatitis after L-asparaginase treatment, and recovered after plasmapheresis.

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2. Case report

48 Years old, female patient was referred to hematology outpatient clinic from the internal medicine outpatient clinic, which she applied with complaints of fatigue and high fever, because of leukocyte count of 42,000 (lymphocyte predominance of 80%), Hb = 6.6 g/dL, Hct of 21%, and thrombocyte count of 76,000. There was no chronic disease history, and no special finding in her familial history. Blastic cell ratio was 40% in her peripheral blood smear. Bone marrow aspiration and biopsy were performed. In her bone marrow evaluation, there were normocellular bone marrow, 90% of blastic cells, and suppression in all lineages. As CD79a, CD19, CD22, CD34 were detected as 92%, 98%, 53%, and 97% in the flow cytometry respectively, the patient was diagnosed with Pro -B ALL, and Hoelzer protocol phase 1 treatment was initiated (L-asparaginase 5000 IU/m² on days 1–14, vincristine 2 mg and daunorubicin 25 mg/m² on days 1–8–15–22, prednisone 60 mg/m² on days 1–28). Mild hepatic enzyme increases were observed in the patient on day 8 of treatment. No pathological sign was encountered in total abdominal ultrasonographic examination of patient, and prednisone dose was decreased by 50%. On the treatment day 11, total bilirubin level was detected as 2.2 mg/dL, and direct bilirubin was detected as 1.5 mg/dL; and they were stable until the day 18. On treatment day 18 (4 days after L-asparaginase treatment was completed), total bilirubin levels were increased progressively (Table 1). No pathological sign was detected in total abdominal ultrasonography and magnetic resonance cholangiopancreatography (MRCP) imaging of the patient. Tests for hepatitis A, hepatitis B, hepatitis C, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) were negative.

On day 26 of chemotherapy, the detected levels were as follows: total bilirubin = 16.9, direct bilirubin = 14.2, AST = 34, ALT = 74, INR = 1.4, PT = 19.1 s, APTT = 28.5 s (Table 1). Patient developed signs of hepatic encephalopathy, so therapeutic plasmapheresis was performed on the patient. A catheter was inserted in the right subclavian vein for plasmapheresis procedure, 4 sessions of plasma exchange were performed with 15 units of fresh frozen plasma (FFP) in each session, so a total of 60 units of FFP

was used. FFP requirement was calculated according to the formula of weight X 70 (100-hematocrit)/100. The procedure was performed by drawing and infusing 120 cc/min plasma. With centrifugation speed of 4500 rpm, plasmapheresis procedure was performed while plasma volume was increased by 20, 30, and 40 mL in the next steps. Volume of plasmapheresis procedure chambers was 125 mL, so 80 mL/min of blood was drawn from the patient at each session, and plasma infusion was performed as 120 mL accompanied by erythrocyte suspension. No complication or reaction was observed during the procedure. After the plasma exchange, total bilirubin level was decreased to 1.5 mg/dL and direct bilirubin level was decreased to 0.3 mg/dL, and hepatic encephalopathy picture was recovered. Remission was detected in bone marrow aspiration and biopsy after Hoelzer protocol phase 1 treatment in the patient. Patient continued to Hoelzer protocol phase 2 treatment without any problems in hepatic function tests and bilirubin levels.

3. Discussion

During plasmapheresis, plasma and cellular components of blood are separated from blood cells together with plasma solutes, such as immunoglobulins. Plasmapheresis can be used for treatment of toxicities caused by some drugs. Plasmapheresis is effective in treatments of drug toxicities of drugs, which are especially bound to plasma proteins. Hemodialysis and hemoperfusion are not effective methods in drug toxicities related to those drugs [7]. L-Asparaginase is an enzyme used in the treatment of ALL. L-Asparagine is an essential amino acid for lymphoid cells and its mechanism of action is to inhibit protein synthesis for lymphoid cells by hydrolyzing L-asparagine to L-aspartate. Hypersensitivity reactions are common during L-asparaginase treatment [4,5]. Other side effects observed during treatment are acute pancreatitis, coagulation disorders, immune suppression and hepatic injury [5]. Additionally, Narazaki et al. reported immediate-type and delayed type hypersensitivity reactions, which developed after L-asparaginase treatment, in a 5-year old ALL patient [8]. Because of these side effects, use of L-asparaginase is limited.

Table 1

Laboratory parameters according to the days of the case.

	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
ALT (U/l)	11	33	15	18	26	81	37	10
AST (U/l)	9	29	43	69	89	111	59	18
ALP	77	73	91	89	97	82	74	61
GGT	145	165	147	167	186	183	157	102
INR	0.96	1.46	1.1	1.19	1.1	0.91	0.91	0.92
Total bilirubin (U/l)	1.0	1.2	1.2	1.07	3.96	4.81	1.52	0.93
Direct bilirubin (U/l)	0.6	0.9	0.7	0.67	3.16	3.98	0.9	0.27
Indirect bilirubin (U/l)	0.4	0.3	0.5	0.3	0.8	0.83	0.62	0.66
Amylase	33	34	48	39	18	30	45	61
Total cholesterol	152	145	176	187	178	201	183	197
Triglyceride	154	159	114	107	93	145	143	154
LDL cholesterol	104	112	142	131	114	107	122	133
HDL cholesterol	34	45	23	21	19	25	21	18

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transpeptidase, INR: International normalized ratio.

Sahoo and Hart reported results of hepatic biopsy, which was performed due to hepatic toxicity developed in 4 patients receiving L-asparaginase treatment due to ALL. One of patients developed fulminant hepatic toxicity after the first dose of L-asparaginase treatment, so hepatic transplantation was performed. However, patient died 1 month after the transplantation. Hepatic toxicities were observed in 2 patients on day 5 of L-asparaginase treatment, whereas in 1 patient on day 10 of the treatment. Hepatic toxicities were recovered in all three patients after L-asparaginase treatment was stopped [9]. In biopsy results of those patients, hepatic steatosis and hepatocyte damage of various degrees were defined.

Mechanism of hepatic toxicity, which is developed due to L-asparaginase treatment, is not accurately known. However, it has been predicted to be caused by deterioration of mitochondrial β -oxidation of hepatic toxicity related to L-asparaginase, and changes in lipoprotein metabolism [10,11].

Ho et al. showed in their study that plasma concentration of L-asparaginase was cumulatively increased as the result of intravenous L-asparaginase application [6].

Fulminant hepatic failure developed 4 days after completion of L-asparaginase treatment in our patient. Because general state of the patient was bad, hepatic biopsy was not performed for diagnosis. Having thought that plasma concentration of L-asparaginase was cumulatively increased as the result of repetitive applications, and thus hepatic toxicity was developed, 4 sessions of therapeutic plasmapheresis were performed on the patient. After the

plasmapheresis treatment was completed, patient recovered from hepatic failure both clinically and laboratory.

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