L-carnitine and Vitamin B Complex for PEG-L-asparaginase-Induced Hepatotoxicity

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ABSTRACT
Asparaginase is a part of combination chemotherapy for acute lymphoblastic leukemia. We present a 58-year-old woman with refractory acute lymphoblastic leukemia who developed asparaginase-induced hepatotoxicity after receiving intravenous PEG-L-asparaginase-based chemotherapy. The patient presented with hyperbilirubinemia and transaminitis. The patient was diagnosed with drug-induced liver injury due to PEG-L-asparaginase after a thorough evaluation for all other causes and received treatment with L-carnitine and vitamin B complex with normalization of liver numbers. Hepatic dysfunction was attributed to depletion of L-asparagine and glutamine, which impairs mitochondrial β-oxidation and induces steatosis. We reiterate the role of L-carnitine and vitamin B complex for the treatment of asparaginase-induced hepatotoxicity.

INTRODUCTION
Asparaginase is used as part of combination chemotherapy for acute lymphoblastic leukemia (ALL). Common adverse effects include hypersensitivity reactions and pancreatitis. Asparaginase-induced hepatotoxicity (AsIH), characterized by hyperbilirubinemia and transaminase elevation, is common (30%–60%), with the severity depending on the dose and duration of therapy. Hepatic dysfunction is attributed to depletion of L-asparagine and glutamine, which impairs mitochondrial β-oxidation and induces steatosis. We will discuss the role of L-carnitine and vitamin B complex as mitochondrial β-oxidation cofactors for the treatment of asparaginase-induced hepatotoxicity. Future prospective studies are needed to confirm the efficacy of L-carnitine and vitamin B complex.

CASE REPORT
A 58-year-old female Jehovah’s witness with B-cell ALL [Philadelphia chromosome negative; t(4; 11) (q21; q23), t(8; 14) (q11.2; q32); bone marrow with 90% blasts; flow cytometry Tdt+/CD34+/CD19+/CD20−/dim CD22+] refractory to first-line therapy with blinatumomab was treated with a second-line regimen consisting of prednisone 60 mg/m2 daily, intravenous PEG-L-asparaginase 2,500 units/m2 single dose, vincristine 2 mg weekly, and intrathecal cytarabine 70 mg single dose. She was also on prophylactic antimicrobials including caspofungin, ciprofloxacin, and acyclovir. Her transaminases were elevated on day 12 of chemotherapy (10 days after a single dose of PEG-L-asparaginase) with aspartate aminotransferase (AST) 132 IU/L, alanine aminotransferase (ALT) 170 IU/L, and total bilirubin 0.9 mg/dL. The next day, bilirubin peaked at 5 mg/dL with direct fraction 4.2. She developed jaundice with dark-colored urine but without hepatomegaly, fever, or skin rash.

Hepatology was consulted, and she was started on L-carnitine 50 mg/kg every 6 hours and vitamin B complex on day 14, and the dose of PEG-L-asparaginase was held. The transaminases improved somewhat before trending up to a peak on day 21 of AST 231 IU/L, ALT 276 IU/L, bilirubin 12.7 (direct 10.3) mg/dL, and alkaline phosphatase (ALP) 1,053 IU/L. We suspected hepatotoxicity secondary to L-asparaginase, hepatic infiltration by B-cell ALL, or reactivation of viral hepatitis as possible etiologies, which necessitated further workup. Polymerase chain reaction for Epstein-Barr virus, Cytomegalovirus, herpes simplex virus, and hepatitis B immunoglobulin M and immunoglobulin G antibodies were negative. Bone marrow biopsy demonstrated a markedly hypocellular bone marrow (10%)
with trilineage hematopoiesis and no increase in blasts. Subsequently, transjugular liver biopsy showed a hepatic venous pressure gradient of 4 mm Hg. Histopathology revealed severe steatohepatitis with severe steatosis and marked ballooning degeneration/foamy change and biliary injury in the form of moderate bile stasis, severe bile duct epithelial injury, and a prominent ductular reaction; there was no liver involvement by B-cell ALL (Figure 1).

Based on the above findings, we made a diagnosis of drug-induced liver injury due to PEG-L-asparaginase and continued therapy with L-carnitine and vitamin B complex. The L-carnitine dose was tapered at chemotherapy day 30 to 4,000 mg every 24 hours for an additional 9 days, with vitamin B complex discontinued on day 39, as well. Her transaminases improved to AST 28 IU/L, ALT 36 IU/L, ALP 101 IU/L, and total bilirubin 0.4 mg/dL at day 52 and remained normal with AST 22 IU/L, ALT 18 IU/L, ALP 88 IU/L, and total bilirubin 0.3 mg/dL at day 93. Subsequently, she was started on a postremission chemotherapy regimen at day 151 with high-dose intravenous methotrexate, leucovorin rescue, vincristine, and intrathecal methotrexate and assessed for potential rechallenge with non-pegylated asparaginase. Her transaminases remained normal with AST 20 IU/L, ALT 13 IU/L, ALP 75 IU/L, and bilirubin 0.4 mg/dL. The patient’s clinical course is summarized in Figure 2.

DISCUSSION

Asparaginase is an enzyme that hydrolyzes the extracellular amino acid L-asparagine and induces apoptosis of lymphoblastic cells by inhibiting protein synthesis. It is a key component of combination chemotherapy for ALL. It is available in the United States as L-asparaginase, a short-acting, Dickeya dadantii-derived formulation and PEG-L-asparaginase, a long-acting, Escherichia coli-derived PEGylated formulation.

The most common deleterious effects of asparaginase therapy include hypersensitivity reactions and pancreatitis, with less common ones including thromboembolic events, immune hemolytic anemia, coagulopathy, nephropathy, neurological dysfunction, metabolic derangements (hypertriglyceridemia), and hepatotoxicity. AsIH (ie, hyperbilirubinemia and transaminase elevation) is common (30%–60%), with high-grade hyperbilirubinemia in 14% of adults. The severity of hepatotoxicity depends on the dose and duration of asparaginase therapy because its enzymatic activity lasts 3–4 weeks. Other risk factors for AsIH include patient age and concurrent use of other hepatotoxic agents.

The presumed mechanism of hepatotoxicity is depletion of the L-asparagine and glutamine pool, causing decreased protein synthesis. This leads to impaired mitochondrial $\beta$-oxidation and accumulation of unoxidized fatty acids in the hepatic parenchyma. Steatosis is typically observed (50%–90%), whereas hepatocyte necrosis is less prominent. The degree of steatosis is reported to be less severe in those receiving PEG-L-asparaginase. A few previously reported cases of L-asparaginase toxicity did mention biliary injury as a prominent feature, and our case confirms their findings. However, it must be emphasized that biliary injury might have been independent of asparaginase toxicity because of some other component of the chemotherapy regimen.

Historically, the treatment of AsIH has been supportive. However, mitochondrial $\beta$-oxidation cofactors such as L-carnitine and vitamin B complex have been described to be useful. L-carnitine is a naturally occurring amino acid derivative that works by facilitating the transport of long-chain fatty acids into the mitochondria, whereas B-complex vitamins serve as cofactors in mitochondrial $\beta$-oxidation. In a rat model of asparaginase-induced steatohepatitis, administration of L-carnitine was successful in reducing elevated liver enzymes to baseline levels. L-carnitine has also been proposed as hepatoprotective against a number of other hepatotoxic medications such as valproic acid and acetaminophen.

There are a few published reports of adult patients with B or T-cell ALL treated with ALL regimens that included L-asparaginase who developed hepatic dysfunction in the form of elevated total bilirubin, ALP, and ALT. The laboratory parameters in these patients improved after 3 to 22 days of
therapy with L-carnitine and vitamin B complex. The L-carnitine dose was 50 mg/kg/d in 4 of 5 reported cases, whereas the fifth patient received a higher dose of 75 mg/kg every 4 hours, which did not lead to expedited hepatic recovery.

Our case supports the efficacy of L-carnitine and vitamin B complex in AsIH. It could be argued that the improvement in transaminases in our case, which occurred within 3–4 weeks of stopping PEG-L-asparaginase, may be because of discontinuation of chemotherapy alone and not a direct effect of L-carnitine and vitamin B complex therapy. However, treatment with L-carnitine and vitamin B complex was warranted in light of significant liver injury. A similar post-treatment pattern of delayed decline in transaminase levels after up to 21 days of being on L-carnitine and vitamin B complex has been previously reported in the literature. We further reinforce the fact that such patients may be able to receive additional doses of asparaginase after recovery of hepatic function, as was seen in another similar case of PEG-L-asparaginase-induced acute hepatic injury. Regardless, there are no existing prospective randomized controlled trials evaluating the use of L-carnitine and vitamin B complex in hepatotoxicity due to asparaginase. Although a pre-existing L-carnitine or vitamin B deficiency may increase the risk of L-asparaginase-induced hepatotoxicity, there is insufficient evidence to support prophylactic use of either L-carnitine or vitamin B.

We recommend the use of L-carnitine (50 mg/kg loading dose, followed by 50 mg/kg/d divided into 6 doses) along with vitamin B complex in suspected cases of L-asparaginase-induced hepatic injury until the transaminases return to baseline values. It may be possible to carefully reintroduce asparaginase if needed to for rescue therapy.

**DISCLOSURES**

Author contributions: S. Arora, J. Klair, and T. Tanaka wrote and edited the manuscript. AM Bellizzi reviewed the histological images. T. Tanaka is the article guarantor.

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