HHS Public Access

Author manuscript

Leuk Lymphoma. Author manuscript; available in PMC 2023 May 14.

Published in final edited form as:

Leuk Lymphoma. 2018 October ; 59(10): 2360–2368. doi:10.1080/10428194.2018.1435873.

Levocarnitine for asparaginase-induced hepatic injury: a multi-institutional case series and review of the literature

Rachael R. Schulte[a], **Manasi V. Madiwale**[b], **Allyson Flower**[c], **Jessica Hochberg**[c], **Michael J. Burke**[d], **Jennifer L. McNeer**[e], **Adam DuVall**[f], **Archie Bleyer**[g]

[a]Department of Pediatrics, Division of Pediatric Hematology/Oncology, Monroe Carell Jr. Children's Hospital, Vanderbilt University Medical Center, Nashville, TN, USA

[b]Division of Pediatric Hematology/Oncology, Children's Hospital and Research Center, Oakland, CA, USA

[c]Department of Pediatrics, Division of Pediatric Hematology, Oncology, and Stem Cell Transplantation, New York Medical College, Valhalla, NY, USA

[d]Department of Pediatrics, Division of Hematology/Oncology/Blood and Marrow Transplantation, Medical College of Wisconsin, Milwaukee, WI, USA

[e]Department of Pediatrics, Section of Pediatric Hematology/Oncology/Stem Cell Transplant, University of Chicago Medical Center, Chicago, IL, USA

[f]Department of Medicine, Division of Hematology and Medical Oncology, and Department of Pediatrics, Division of Pediatric Hematology/Oncology, OHSU Doernbecher Children's Hospital, Oregon Health and Science University, Portland, OR, USA

[g]Department of Radiation Medicine, Oregon Health and Science University, Portland, OR, USA

Abstract

Asparaginase, an important treatment component for acute lymphoblastic leukemia (ALL), causes severe hepatotoxicity in some patients. Levocarnitine is a mitochondrial co-factor that can potentially ameliorate the mitochondrial toxicity of asparaginase. In this retrospective case series, we describe the clinical presentation and management of six pediatric and young adult patients (mean age 12.7, range 9–24 years) with ALL who developed Grade 3–4 hyperbilirubinemia following administration of asparaginase as part of induction/re-induction therapy. Five of these patients were treated with levocarnitine with subsequent improvement of hyperbilirubinemia, while one patient was given levocarnitine prophylactically during induction and developed Grade 3 hyperbilirubinemia, but did not require therapy adjustments or delays. Increased awareness in the pediatric oncology community regarding asparaginase-associated hepatic toxicity and the potential role of levocarnitine in management is warranted.

CONTACT Rachael R. Schulte rachael.schulte@vanderbilt.edu Department of Pediatrics, Division of Pediatric Hematology/Oncology, Monroe Carell Jr. Children's Hospital, Vanderbilt University Medical Center, 397 PRB, 2220 Pierce Ave, Nashville, TN 37232; 615-936-5314; MD; 397 PRB, 2220 Pierce Avenue, Nashville, TN 37232, USA.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article online at https://doi.org/10.1080/10428194.2018.1435873.

Keywords

Asparaginase; hepatic injury; hyperbilirubinemia; ALL; leukemia; levocarnitine

Introduction

Asparaginase has been an integral component of multi-agent chemotherapy used in the treatment of children with acute lymphoblastic leukemia (ALL). Although historically asparaginase has been used less commonly in adults, its use in adult patients has been increasing following reports of better treatment outcomes using pediatric-inspired regimens that include asparaginase [1–4]. Toxicities commonly associated with asparaginase therapy include allergy, hyperglycemia, coagulopathy, hyperammonemia, liver toxicity, hypertriglyceridemia, and pancreatitis [5]. Toxicities that are severe enough (e.g. anaphylaxis, hemorrhagic pancreatitis) may lead to discontinuation of asparaginase therapy. Elimination of asparaginase therapy has been associated with worse outcomes, suggesting that this chemotherapeutic agent remains critically important in the cure of patients with ALL [6].

Asparaginase exerts its anti-leukemic effects by depleting circulating pools of asparagine and, to a lesser extent, glutamine. Leukemia cells lack asparagine synthase and rely solely on the host's asparagine stores for protein synthesis [7]. Amino acid depletion leads to reductions in protein synthesis, resulting in mitochondrial dysfunction, metabolic stress, and generation of reactive oxygen species, ultimately causing apoptosis of leukemia cells [8]. The duration of asparagine depletion depends on the drug preparation (native *Escherichia coli* asparaginase, PEGylated *E. coli* asparaginase (PEG-asparaginase), or *Erwinia* asparaginase) and form of administration (intravenous versus intramuscular). The pharmacokinetics of each preparation are different, which affects the amount of time after administration during which patients are at risk for adverse effects [9].

Asparaginase-induced liver toxicity ranges from mild elevation of bilirubin and/or transaminases to fulminant hepatic failure, multi-organ dysfunction, and death [9]. Apart from the morbidity and mortality associated with severe hepatic injury, this drug toxicity can lead to subsequent chemotherapy delays. While the incidence of high-grade liver toxicity is lower in pediatric patients compared to adults [1], serious cases in children have been reported [9–11]. Presently, there is no standard of care for managing patients with asparaginase-associated hepatotoxicity, although emerging evidence suggests that levocarnitine (L-carnitine) may be a safe and effective therapy for asparaginase-induced liver injury [12–16].

In this case series, we present six patients (five pediatric, one young adult) with newly diagnosed or relapsed B-cell ALL; five of these patients developed Grade 4 hyperbilirubinemia following PEG-asparaginase and were treated with L-carnitine, and one patient was given L-carnitine prophylactically. We describe their clinical characteristics and course and review the literature regarding use of L-carnitine as prophylaxis or treatment of asparaginase-associated liver injury (Table 1).

Methods

All patients received PEG-asparaginase doses at 2500 IU/m^2 intravenously (IV) over 1–2 h, with no maximum dose. Patients with newly diagnosed high risk (HR) B-ALL were treated on the Children's Oncology Group (COG) study AALL1131. Patient 4 with relapsed B-ALL was treated on the COG study AALL1331 (Table 2). Table 3 contains details of carnitine therapy for each patient. Institutional review board approval was obtained at each site for data collection.

Reference ranges for lab values utilized in the text are as follows: total bilirubin 0.05–0.6 mg/dL; conjugated bilirubin 0.1–0.3 mg/dL; aspartate aminotransferase (AST) 18–36 units/L; alanine aminotransferase (ALT) 8–24 units/L; alkaline phosphatase (141–460 units/L); prothrombin time (PT) 11.8–14.5 s; partial thromboplastin time (PTT) 23–34 s; lipase 4–39 units/L; ammonia 18–72 μmol/L. In all cases, the concern for asparaginase-induced liver toxicity was a clinical diagnosis made based on hepatic/cholestatic abnormalities that started after PEG-asparaginase administration with no other apparent cause. "Baseline" refers to the most recent laboratory values prior to the administration of PEG-asparaginase. For each patient, hyperbilirubinemia and transaminitis were assigned a severity grade according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Case descriptions

Case 1—Patient 1 was an 11-year-old Hispanic male with newly diagnosed HR B-ALL. Baseline labs included total bilirubin 0.8 mg/dL, AST 188 units/L, AST 314 units/L, PT 13.5 s, PTT 31.3 s. On Day 22 of induction (18 d after PEG-asparaginase), he presented with weakness, peripheral edema, scleral icterus, jaundice, total bilirubin 16.6 mg/dL, and conjugated bilirubin 11.3 mg/dL, consistent with Grade 4 hyperbilirubinemia. His AST (59 units/L) and ALT (140 units/L) had decreased, but PT/ PTT had risen to 17.0 and 41.6 s, respectively. Lipase was normal (23 units/L). Day 22 vincristine and daunorubicin were held secondary to hyperbilirubinemia. Abdominal CT showed diffuse hepatic steatosis and ascites with mild pancreatic duct dilation but no pancreatic mass. Abdominal ultrasound showed no thrombosis or signs of veno-occlusive disease.

L-carnitine therapy was started on Day 23 (50 mg/kg/d) and increased the next day (100 mg/kg/d) based on literature review. Lactulose and ursodiol were started on Days 24 and 25, respectively. Viral hepatitis testing was negative. PT/PTT rose to 23.4 and 57.7 s, respectively, on Day 26. Bilirubin peaked on Day 26 (total bilirubin 24.3 mg/dL, conjugated bilirubin 17.5 mg/dL). On Day 28, he developed altered mental status (peak ammonia 71 μmol/L on Day 29) which resolved with supportive care. His end of induction (Day 29) bone marrow evaluation demonstrated remission with no evidence of minimal residual disease (MRD) by flow cytometry (<0.01% blasts). Over time the patient's clinical status improved; bilirubin decreased beginning 4 d after the start of L-carnitine though never completely normalized (total bilirubin nadir 9.7 mg/dL, conjugated 7.1 mg/dL on Day 42).

On Day 39 of therapy, the patient had worsening abdominal pain and elevated lipase (70 units/L). Abdominal CT demonstrated a 34-cm pancreatic pseudocyst, managed non-

surgically. His clinical status improved and, due to downtrending bilirubin, L-carnitine and vitamin B complex therapy were discontinued by the treating physician on Day 41. However, he had an increase in his abdominal pain 3 d later (Day 44) associated with altered mental status and hypotension which prompted transfer to the pediatric intensive care unit, intubation, and initiation of vasopressors. His labs had worsened including AST 6297 units/L, ALT 1918 units/L, ammonia 116 μmol/L, PT 30.1 s, PTT 79.9 s, lipase 435 units/L, hemoglobin 5.9 g/dL (down from 8.2 g/dL less than 24 h prior), and WBC 78.2 × 10^3/μL (flow cytometry confirmed absence of blasts). Abdominal CT showed hemorrhage into the pancreatic pseudocyst. His clinical status continued to decline and he died on Day 45.

Case 2—Patient 2 was an 11-year-old Hispanic female with newly diagnosed HR B-ALL. She was enrolled on an anti-coagulant (apixaban) supportive care study in addition to AALL1131. Baseline labs included total bilirubin 1.0 mg/dL, AST 26 units/L, ALT 117 units/L, and normal PT/PTT. On Induction Day 17 (13 d after PEG-asparaginase), PT/PTT were both unmeasurable (upper limit of detection 143.7 s for PT, 133.6 s for PTT) and apixaban was stopped. PT/PTT downtrended to 14.0 and 43.4 s, respectively, on Day 18, normalizing by Day 28. Bilirubin began to rise on Day 14 (10 d after PEG-asparaginase); peak total bilirubin was 10.2 mg/dL with conjugated bilirubin 7.5 mg/dL on Day 25, consistent with Grade 4 hyperbilirubinemia. Transaminases also rose (peak AST 108 units/L, ALT 257 units/L on Day 24). Vincristine and daunorubicin (Day 22) were held due to hyperbilirubinemia.

Due to the rise in bilirubin and transaminases, L-carnitine was started on Day 27. Total bilirubin had begun to downtrend just prior to the start of L-carnitine, but this trend became more pronounced after its initiation; total bilirubin normalized over the next several weeks, reaching <2 mg/dL on Day 46. AST/ALT normalized by Day 58. L-carnitine was continued until 2 weeks after the next dose of PEG-asparaginase on Day 15 of consolidation therapy. During this time, the maximum total bilirubin was 3.3 mg/dL with conjugated bilirubin 2.4 mg/dL. L-carnitine was resumed prophylactically on Day 40 of consolidation prior to Day 43 PEG-asparaginase and continued through Day 56 during which time total bilirubin peaked at 1.3 mg/ dL (Day 53). There were no hyperbilirubinemia-related therapy delays during consolidation. The patient ultimately came off protocol due to persistent MRD after consolidation and proceeded to hematopoietic stem cell transplant.

Case 3—Patient 3 was a 10-year-old Brazilian male diagnosed with HR B-ALL. Baseline labs included total bilirubin 0.6 mg/dL, ALT 26 units/L. On Day 15 (11 d after PEG-asparaginase), the patient presented with scleral icterus, total bilirubin 2.8 mg/dL, and conjugated bilirubin 0.1 mg/dL. Increasing hyperbilirubinemia was noted over the next several days (peak total bilirubin 42.4 mg/dL and conjugated bilirubin 28.1 mg/dL on Day 31, consistent with Grade 4 hyperbilirubinemia), along with elevated ALT (peak 216 units/L on Day 31, consistent with Grade 3 transaminitis). Day 22 vincristine and daunorubicin were held due to hyperbilirubinemia. Abdominal imaging showed hepatic steatosis without other pathology.

Due to hyperbilirubinemia, consolidation therapy was delayed. L-carnitine was started on Induction Day 33. Total bilirubin decreased from 39.3 mg/dL (Day 33) to 24.6 mg/dL after

6 d of L-carnitine. Consolidation therapy was initiated on Day 40 after the start of Induction and L-carnitine was continued; total bilirubin continued to decrease but did not fall below 2 mg/dL until Day 20 of Consolidation. The patient did not receive Consolidation Day 15 PEG-asparaginase due to hyperbilirubinemia but did receive future doses as scheduled. The treating clinician elected to continue the patient on oral L-carnitine therapy through the end of delayed intensification. He successfully tolerated subsequent doses of PEG-asparaginase while on L-carnitine prophylaxis with a maximum total bilirubin of 1.5 mg/dL.

Case 4—Patient 4 was a 9-year-old Caucasian female with relapsed B-ALL. Total bilirubin at the time of relapse was 0.2 mg/dL. On re-Induction Day 15 (12 d after PEG-asparaginase), her total bilirubin had risen to 1.6 mg/dL and continued to rise over the next week (total bilirubin peaked at 6.7 mg/dL and conjugated bilirubin at 5.9 mg/dL on Day 22). Transaminitis was noted on Day 22 (AST 366 units/L, ALT 832 units/L). Peak bilirubin and transaminase values were consistent with Grade 4 and Grade 3–4 toxicity, respectively. Day 22 vincristine was held due to hyperbilirubinemia.

IV L-carnitine was started on Day 22 and continued for 5 d, then was replaced by oral L-carnitine. Bilirubin and transaminase values gradually improved (total bilirubin 2.8 mg/dL, conjugated bilirubin 1.5 mg/dL, AST 46 units/L, ALT 128 units/L on Day 29). By the time the next PEG-asparaginase dose was due on Day 8 of Block 2 therapy, her total bilirubin was 1.2 mg/dL and conjugated bilirubin 0.5 mg/dL. Oral L-carnitine was continued until 2 d prior to the Day 8 Block 2 PEG-asparaginase dose after which a combination of IV and oral L-carnitine were used around the time of PEG-asparaginase dosing (see Table 3 for details). Maximum total bilirubin during the remainder of Block 2 therapy was 1.1 mg/dL and no additional chemotherapy doses were held or adjusted. The patient received *Erwinia* asparaginase, per protocol, during Block 3 therapy without L-carnitine and had no further evidence of hepatotoxicity.

Case 5—Patient 5 was an 11-year-old Caucasian male who presented with newly diagnosed HR B-ALL. Baseline labs included total bilirubin 0.4 mg/dL, conjugated bilirubin 0.1 mg/dL, AST 41 units/L, and ALT 23 units/L. A rise in total bilirubin was noted on Day 15 (11 d after PEG-asparaginase), peaking at 17.3 mg/dL with conjugated bilirubin 13.2 mg/dL on Day 25, consistent with Grade 4 hyperbilirubinemia. Transaminases also rose, peaking at AST 144 units/L and ALT 303 units/L on Day 20. Ultrasound on Day 21 showed increased liver size and echogenicity, most consistent with steatosis, with no other pathology identified. Vincristine and daunorubicin (Day 22) were held due to hyperbilirubinemia.

L-carnitine was started on Day 25 due to hyperbilirubinemia and total bilirubin began to downtrend (10.1 mg/dL on Day 28, 2.0 mg/dL on Day 40). For future doses of PEG-asparaginase, he received oral L-carnitine prophylaxis for 1 week before and after each dose without any hepatotoxicity. Maximum total bilirubin with future doses was 1.3 mg/dL with conjugated bilirubin 0.1 mg/dL. He did not require any additional alterations to his chemotherapy regimen.

Case 6—Patient 6 was a 24-year-old Hispanic male who presented with newly diagnosed HR B-ALL. Due to his older age, obesity (BMI > 30), and moderate elevation of his AST

(135 units/L) and ALT (92 units/L) at diagnosis, a liver ultrasound was performed which confirmed hepatic steatosis. The patient was placed on oral L-carnitine prophylaxis on Day 1 of Induction therapy for prevention of asparaginase-associated hepatotoxicity. AST/ALT normalized quickly after initiation of chemotherapy. PTT was mildly prolonged (39.1 s) at diagnosis but normalized (30.1 s) by Day 3, prior to PEG-asparaginase.

On Induction Day 4, just prior to PEG-asparaginase, total bilirubin was 2.5 mg/dL and conjugated bilirubin 0.6 mg/dL. By Day 7 (3 d after PEG-asparaginase), total bilirubin had peaked at 4.0 mg/dL, conjugated bilirubin 1.3 mg/dL, consistent with Grade 3 hyperbilirubinemia. The patient remained on oral L-carnitine through Day 29 of Induction therapy and was able to receive all scheduled chemotherapy without delays or dose adjustments. After successfully completing induction and achieving complete remission with MRD negativity, the patient proceeded to consolidation therapy including 14 d of prophylactic L-carnitine starting the day of each PEG-asparaginase dose. Three scheduled doses of PEG-asparaginase were administered without any evidence of hepatotoxicity. PEG-asparaginase was held starting on Day 43 of delayed intensification due to pancreatitis but he received all other chemotherapy as planned.

Discussion

Previous studies have reported elevation of transaminases and/or bilirubin following asparaginase therapy in as many as 30–60% of patients with ALL [1]. Hepatic steatosis has been demonstrated on liver biopsies from both pediatric and adult patients following asparaginase therapy [17], with steatosis lasting for weeks to months [18]. Additionally, there are case reports of severe liver toxicity occurring in adults with ALL [13–16,19–22], with any degree of toxicity potentially causing delays in subsequent chemotherapy which can affect clinical outcomes.

Asparaginase-induced hepatic toxicity occurs more frequently in overweight/obese patients and in those of Hispanic ethnicity [2]. The relationship between obesity and chemotherapy-induced hepatotoxicity has also been reported in pediatric ALL patients [23]. This epidemiological finding is possibly related to high rates of non-alcoholic steatohepatitis (NASH) in both Hispanic and obese patients [24], with the hypothesis that pre-existing NASH predisposes patients to asparaginase-induced hepatotoxicity due to the finding that patients with NASH have altered mitochondrial respiratory chain function, including perturbations in carnitine shuttling [25]. In mice, obesity causes activation of maladaptive pathways in hepatocytes in response to asparaginase-induced metabolic stress, leading to reduced ability of the cells to be rescued from this stress by normal pathways [26]. Of the patients described in this report, four of six (67%) were of Hispanic or Brazilian ethnicity and five of six (83%) were obese per age-specific standards, consistent with these associations.

Although the mechanism of asparaginase-induced liver toxicity is not clear, several hypotheses have been proposed. Amino acid depletion, such as that occurring with asparaginase therapy, causes metabolic stress in cells, preventing synthesis of vital proteins and resulting in generation of reactive oxygen species that can trigger apoptosis.

Mitochondrial stress due to reduced protein synthesis can lead to altered lipid metabolism with accumulation of unoxidized fatty acids which are damaging to cells [1,5,8]. Drug-induced mitochondrial dysfunction caused by amino acid depletion and resulting impairment in energy production leads to microvesicular steatosis, hepatic necrosis, or apoptosis [27], all of which may play a role in asparaginase-induced hepatotoxicity. It has been suggested that the asparaginase-induced depletion of glutamine, rather than asparagine, is responsible for hepatotoxicity, which is supported by reduced rates of hepatotoxicity in mice treated with a preparation of asparaginase that has no glutaminase activity [28,29]. Asparagine also regulates mRNA expression of critical signaling molecules, including those from the Toll-like receptor (TLR) family (TLR4, IL-1 receptor-associated kinase 1, TNF-α receptor-associated factor 6), nucleotide-binding oligomerisation domain (SOD) protein, serine/threonine-protein kinase 2, and NF-kB p65 [30]. Patients with variant rs4880 in the SOD2 gene, a key mitochondrial enzyme that protects cells against reactive stress, have increased hepatotoxicity following asparaginase-based treatment [8].

Carnitine is an endogenous molecule that shuttles fatty acids into and out of mitochondria and serves an important role in fatty acid oxidation and energy production under normal conditions. During times of metabolic stress, such as amino acid depletion, accumulation of mitochondrial organic acid intermediates can occur. Carnitine serves as a buffer for these excessive organic acids and helps to maintain normal mitochondrial function and cell viability under abnormal cellular conditions [31]. Through this buffering function, carnitine may help to overcome the mitochondrial dysfunction that is believed to play a role in asparaginase-induced hepatotoxicity.

L-carnitine has been used to treat patients with both primary and secondary carnitine deficiencies. In addition, L-carnitine along with a vitamin B complex has been reported to mitigate hepatotoxicity associated with chronic use of nucleoside reverse transcriptase inhibitors [32,33]. L-carnitine has also been used for management of acute valproic acid overdose in children [34,35] at doses of 90 mg/kg/d [34] to 150 mg/kg/d (maximum 3 g per day) [35] IV for patients with evidence of hepatotoxicity. The product monograph suggests dosing of 50–100 mg/kg/d (maximum 3 g per day), depending on clinical response, for infants and children with inborn errors of metabolism [36].

The most common adverse effects of oral and IV L-carnitine are gastrointestinal (nausea, vomiting, diarrhea, abdominal pain) [36–39]. For IV L-carnitine, a number of other adverse effects from clinical trials in chronic hemodialysis patients have been reported, but it is unclear how many of these are related to L-carnitine versus the patients' underlying disease [36]. Additional reported side effects from trials using oral L-carnitine include musculoskeletal complaints, rash, fatigue, body odor, and headache [37–39].

L-carnitine reverses asparaginase-induced liver steatosis in rats [12], and case reports in adult patients with ALL suggest efficacy against this toxicity [13–16]. Most of the patients in these reports treated with L-carnitine had rapid reversal of their laboratory abnormalities and normalization of their clinical status (Table 4). In the referenced studies, L-carnitine was dosed IV at either 50 mg/kg/d [13,14,16] or 75 mg/kg/d [15], either alone [14] or

in combination with a vitamin B complex [13,15,16]. However, these reports have been exclusively in adult patients.

Recent studies in pediatric patients with ALL report asparaginase-associated hepatotoxicity (Grade 3 or 4) in 4–8% of patients depending on the preparation of asparaginase given [40–42]. However, there are no controlled studies published on the role of L-carnitine in the treatment of asparaginase-induced liver toxicity. We are not aware of any case reports/series on L-carnitine for this indication in children with ALL, but a retrospective analysis of 15 adult patients with ALL treated at Moffitt Cancer Center (Tampa, FL) who received L-carnitine prophylactically to prevent asparaginase-associated toxicity is underway (2017 personal communication, Bijal Shah and Leidy Isenalumhe).

The use of L-carnitine in patients with cancer has raised concerns for an anti-tumor effect; however, several studies failed to show any tumor protective effect of L-carnitine in either leukemia cells treated with asparaginase [12] or carcinoma cells treated with doxorubicin [43], epirubicin [44], or mitoxantrone [45]. In mice, Niang et al. [45] found that L-carnitine helped to overcome mitoxantrone resistance and actually improved the cytotoxicity of this agent.

As demonstrated by the six pediatric and young adult patients in our series, liver toxicity attributed to asparaginase therapy seems to be prominently related to obesity and/or Hispanic ethnicity, although it can also occur in patients who do not fit these clinical criteria, such as those with hepatic steatosis from another cause. In summary, L-carnitine was well tolerated in all of our patients and, importantly, five patients showed improvement in their degree of hyperbilirubinemia following initiation of L-carnitine as treatment and one patient with risk factors for hepatotoxicity received L-carnitine prophylaxis and was able to receive all chemotherapy as scheduled. Except for a single patient death from multi-organ failure, all patients successfully proceeded to their next treatment phase and were able to tolerate future doses of PEG-asparaginase. Pancreatic toxicity appears not to be preventable with carnitine at the dose schedule used in our series since Patient 1 developed a pancreatic pseudocyst and Patient 6 developed pancreatitis while receiving L-carnitine.

Based on our literature review and personal experience, we suggest the following regimen for treatment of asparaginase-induced hepatotoxicity in patients with ALL: L-carnitine loading dose of 100 mg/kg followed by maintenance dosing of 50 mg/kg/d divided every 8–12 h until laboratory values (e.g. bilirubin, ALT) normalize. If labs do not begin to improve within 3 d on this regimen, or if the patient has a more severe presentation in terms of laboratory abnormalities or clinical symptoms of hepatotoxicity, dosing of 100 mg/kg/d (maximum 3 g per day) divided every 8–12 h should be considered. IV L-carnitine therapy is considered most appropriate for initial management of hepatotoxicity. For prophylaxis, high-risk patients could be given IV or oral L-carnitine at the same dosing as above throughout induction therapy, when risk seems to be highest. Clinicians may consider using L-carnitine for prophylaxis with future doses of PEG-asparaginase; however, no published data exist to guide further management. Given the recent experience at Moffitt Cancer Center cited above, this dosing regimen is expected to be effective and well tolerated in both pediatric and adult patients. The role of vitamin B complex in conjunction with L-carnitine for

this indication is unclear; given the number of studies which showed improvement with carnitine alone, we suspect that L-carnitine is the more efficacious agent, though vitamin B therapy has a low risk of adverse effects and could be considered for severe cases. Formal studies into the role of L-carnitine in the prophylaxis or treatment of asparaginase-induced hepatotoxicity in pediatric patients with ALL should be considered.

Acknowledgements

M. J. B. is the Consultant for Shire Pharmaceuticals, JAZZ Pharmaceuticals, Speaker's Bureau for Shire Pharmaceuticals and JAZZ Pharmaceuticals.

References

[1]. Stock W, Douer D, DeAngelo DJ, et al. Prevention and management of asparaginase/pegasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel. Leuk Lymphoma. 2011;52:2237–2253. [PubMed: 21827361]

[2]. Aldoss I, Douer D, Behrendt CE, et al. Toxicity profile of repeated doses of PEG-asparaginase incorporated into a pediatric-type regimen for adult acute lymphoblastic leukemia. Eur J Haematol. 2016;96:375–380. [PubMed: 26095294]

[3]. DeAngelo DJ, Stevenson KE, Dahlberg SE, et al. Long-term outcome of a pediatric-inspired regimen used for adults aged 18–50 years with newly diagnosed acute lymphoblastic leukemia. Leukemia. 2015;29: 526–534. [PubMed: 25079173]

[4]. Stock W, La M, Sanford B, et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. Blood. 2008;112:1646–1654. [PubMed: 18502832]

[5]. Raetz EA, Salzer WL. Tolerability and efficacy of L-asparaginase therapy in pediatric patients with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2010;32:554–563. [PubMed: 20724951]

[6]. Silverman LB, Gelber RD, Dalton VK, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91–01. Blood. 2001;97:1211. 8. [PubMed: 11222362]

[7]. Asselin B, Rizzari C. Asparaginase pharmacokinetics and implications of therapeutic drug monitoring. Leuk Lymphoma. 2015;56:2273–2280. [PubMed: 25586605]

[8]. Alachkar H, Fulton N, Sanford B, et al. Expression and polymorphism (rs4880) of mitochondrial superoxide dismutase (SOD2) and asparaginase induced hepatotoxicity in adult patients with acute lymphoblastic leukemia. Pharmacogenomics J. 2017;17:274–279. [PubMed: 27019981]

[9]. Hijiya N, van der Sluis IM. Asparaginase-associated toxicity in children with acute lymphoblastic leukemia. Leuk Lymphoma. 2016;57:748–757. [PubMed: 26457414]

[10]. Place AE, Stevenson KE, Vrooman LM, et al. Intravenous pegylated asparaginase versus intramuscular native Escherichia coli L-asparaginase in newly diagnosed childhood acute lymphoblastic leukaemia (DFCI 05–001): a randomised, open-label phase 3 trial. Lancet Oncol. 2015;16:1677–1690. [PubMed: 26549586]

[11]. Ozdemir ZC, Turhan AB, Eren M, et al. Is N-acetylcysteine infusion an effective treatment option in L-asparaginase associated hepatotoxicity? Blood Res. 2017;52:69–71. [PubMed: 28401107]

[12]. Roesmann A, Afify M, Panse J, et al. L-carnitine ameliorates L-asparaginase-induced acute liver toxicity in steatotic rat livers. Chemotherapy. 2013;59:167–175. [PubMed: 24192517]

[13]. Al-Nawakil C, Willems L, Mauprivez C, et al. Successful treatment of l-asparaginase-induced severe acute hepatotoxicity using mitochondrial cofactors. Leuk Lymphoma. 2014;55:1670–1674. [PubMed: 24090500]

[14]. Alshiekh-Nasany R, Douer D. L-carnitine for treatment of pegasparaginase-induced hepatotoxicity. Acta Haematol. 2016;135:208–210. [PubMed: 26841296]

[15]. Lu G, Karur V, Herrington JD, et al. Successful treatment of pegaspargase-induced acute hepatotoxicity with vitamin B complex and L-carnitine. Proc (Bayl Univ Med Cent). 2016;29:46–47. [PubMed: 26722167]

[16]. Blackman A, Boutin A, Shimanovsky A, et al. Levocarnitine and vitamin B complex for the treatment of pegaspargase-induced hepatotoxicity: a case report and review of the literature. J Oncol Pharm Pract. 2017;Jan 1.

[17]. Sahoo S, Hart J. Histopathological features of L-asparaginase-induced liver disease. Semin Liver Dis. 2003;23:295–299. [PubMed: 14523682]

[18]. Pratt CB, Johnson WW. Duration and severity of fatty metamorphosis of the liver following L-asparaginase therapy. Cancer. 1971;28:361–364. [PubMed: 5109448]

[19]. Bilgir O, Calan M, Bilgir F, et al. An experience with plasma exchange treatment of acute lymphoblastic leukemia in a case with fulminant hepatitis related to L-asparaginase. Transfus Apher Sci. 2013;49:328–330. [PubMed: 23871581]

[20]. Bodmer M, Sulz M, Stadlmann S, et al. Fatal liver failure in an adult patient with acute lymphoblastic leukemia following treatment with L-asparaginase. Digestion. 2006;74:28–32. [PubMed: 16988508]

[21]. Okamura A, Nishimura M, Sanada Y, et al. L-Asparaginase-induced fulminating liver dysfunction. Int J Hematol. 2013;98:6–7. [PubMed: 23702916]

[22]. Jenkins R, Perlin E. Severe hepatotoxicity from Escherichia coli L-asparaginase. J Natl Med Assoc. 1987;79:775. [PubMed: 3305969]

[23]. Orgel E, Sposto R, Malvar J, et al. Impact on survival and toxicity by duration of weight extremes during treatment for pediatric acute lymphoblastic leukemia: a report from the Children's Oncology Group. J Clin Oncol. 2014;32:1331–1337. [PubMed: 24687836]

[24]. Schneider AL, Lazo M, Selvin E, et al. Racial differences in nonalcoholic fatty liver disease in the U.S. population. Obesity (Silver Spring). 2014;22:292–299. [PubMed: 23512725]

[25]. Perez-Carreras M, Del Hoyo P, Martin MA, et al. Defective hepatic mitochondrial respiratory chain in patients with nonalcoholic steatohepatitis. Hepatology. 2003;38:999–1007. [PubMed: 14512887]

[26]. Nikonorova IA, Al-Baghdadi RJT, Mirek ET, et al. Obesity challenges the hepatoprotective function of the integrated stress response to asparaginase exposure in mice. J Biol Chem. 2017;292:6786–6798. [PubMed: 28242759]

[27]. Labbe G, Pessayre D, Fromenty B. Drug-induced liver injury through mitochondrial dysfunction: mechanisms and detection during preclinical safety studies. Fundam Clin Pharmacol. 2008;22:335–353. [PubMed: 18705745]

[28]. Durden DL, Salazar AM, Distasio JA. Kinetic analysis of hepatotoxicity associated with antineoplastic asparaginases. Cancer Res. 1983;43:1602–1605. [PubMed: 6339039]

[29]. Reinert RB, Oberle LM, Wek SA, et al. Role of glutamine depletion in directing tissue-specific nutrient stress responses to L-asparaginase. J Biol Chem. 2006;281:31222–31233. [PubMed: 16931516]

[30]. Wu H, Liu Y, Pi D, et al. Asparagine attenuates hepatic injury caused by lipopolysaccharide in weaned piglets associated with modulation of Toll-like receptor 4 and nucleotide-binding oligomerisation domain protein signalling and their negative regulators. Br J Nutr. 2015;114:189–201. [PubMed: 26079268]

[31]. Rebouche CJ, Paulson DJ. Carnitine metabolism and function in humans. Annu Rev Nutr. 1986;6:41–66. [PubMed: 3524622]

[32]. Brinkman K, Vrouenraets S, Kauffmann R, et al. Treatment of nucleoside reverse transcriptase inhibitor-induced lactic acidosis. AIDS. 2000;1;14:2801–2802.

[33]. Claessens YE, Cariou A, Chiche JD, et al. L-carnitine as a treatment of life-threatening lactic acidosis induced by nucleoside analogues. AIDS. 2000;14:472–473. [PubMed: 10770558]

[34]. Russell S Carnitine as an antidote for acute valproate toxicity in children. Curr Opin Pediatr. 2007;19: 206–210. [PubMed: 17496767]

[35]. Perrott J, Murphy NG, Zed PJ. L-carnitine for acute valproic acid overdose: a systematic review of published cases. Ann Pharmacother. 2010;44:1287–1293. [PubMed: 20587742]

[36]. Product monograph – Carnitor (levocarnitine) oral and injection. Gaithersburg (MD): Sigma-Tau Pharmaceuticals Inc.; 2015 [updated 2015 April; 2017 May 12]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/018948s026,019257s012,020182s013lbl.pdf

[37]. Hong ES, Kim EK, Kang SM, et al. Effect of carnitineorotate complex on glucose metabolism and fatty liver: a double-blind, placebo-controlled study. J Gastroenterol Hepatol. 2014;29:1449–1457. [PubMed: 24611967]

[38]. Malaguarnera M, Gargante MP, Russo C, et al. L-carnitine supplementation to diet: a new tool in treatment of nonalcoholic steatohepatitis–a randomized and controlled clinical trial. Am J Gastroenterol. 2010; 105:1338–1345. [PubMed: 20068559]

[39]. Jun DW, Kim BI, Cho YK, et al. Efficacy and safety of entecavir plus carnitine complex (GODEX®) compared to entecavir monotherapy in patient with ALT elevated chronic hepatitis B: randomized, multicenter open-label trials. The GOAL study. Clin Mol Hepatol. 2013;19:165–172. [PubMed: 23837141]

[40]. Avramis VI, Sencer S, Periclou AP, et al. A randomized comparison of native *Escherichia coli* asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study. Blood. 2002;99:1986–1994. [PubMed: 11877270]

[41]. Dinndorf PA, Gootenberg J, Cohen MH, et al. FDA drug approval summary: pegaspargase (oncaspar) for the first-line treatment of children with acute lymphoblastic leukemia (ALL). Oncologist. 2007;12:991–998. [PubMed: 17766659]

[42]. Duval M, Suciu S, Ferster A, 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;99:2734–2739. [PubMed: 11929760]

[43]. Sayed-Ahmed MM, Shaarawy S, Shouman SA, et al. Reversal of doxorubicin-induced cardiac metabolic damage by L-carnitine. Pharmacol Res. 1999;39:289–295. [PubMed: 10208759]

[44]. Delaney CE, Hopkins SP, Addison CL. Supplementation with L-carnitine does not reduce the efficacy of epirubicin treatment in breast cancer cells. Cancer Lett. 2007;252:195–207. [PubMed: 17275999]

[45]. Niang M, Melka M, Stoklasova A, et al. Evaluation of the antineoplastic activity of mitoxantrone-L-carnitine combination therapy on an experimental solid form of ehrlich tumour in mice. Pharmacol Res. 2006; 54:447–451. [PubMed: 17049876]

Table 1.

Patient demographics.

Patient	Age (years)	Sex	Ethnicity	BMI (percentile)[a]
1	11	Male	Hispanic	35.3 (>99)
2	11	Female	Hispanic	30 (96)
3	10	Male	Brazilian	19.5 (81)
4	9	Female	Caucasian	19.7 (91)
5	11	Male	Caucasian	17.5 (50)
6	24	Male	Hispanic	39.6 (>99)

BMI: body mass index.

[a]For pediatric patients, the BMI percentile for age according to the Centers for Disease Control and Prevention (CDC) is listed. In pediatric patients, obesity is defined as BMI greater than the 95th percentile for age; in adult patients, obesity is defined as BMI>30.

Table 2.

Chemotherapy regimen details.

Protocol	Regimen details
COG AALL1131 induction	• Vincristine 1.5mg/m^2 (maximum 2 mg) IV on Days 1,8, 15, 22 • Daunorubicin 25mg/m^2 IV on Days 1, 8, 15, 22 • Prednisone 30mg/m^2/dose PO BID on Days 1–28 • PEG-Asparaginase 2500 IU/m^2 IV on Day 4 • Cytarabine IT on Day 1 or within 72 h of start of protocol therapy • Methotrexate IT on Days 8 and 29 for CNS1/2 patients; on Days 8, 15, 22, and 29 for CNS3 patients • Consolidation therapy begins on Day 36 after the start of Induction if laboratoryparameters are met
COG AALL1131 consolidation	• PEG-Asparaginase 2500 IU/m^2 IV on Days 15 and 43 • Remainder of therapy is based on risk assignment (high versus very high risk) and randomization to control versus experimental arms
COG AALL1331 Block 1 (All patients)	• Mitoxantrone 10mg/m^2 IV on Days 1, 2 • Vincristine 1.5mg/m^2 (maximum 2 mg) IV on Days 1,8, 15, 22 • PEG-Asparaginase 2500 IU/m^2 on Days 3, 17 • Dexamethasone 10mg/m^2/dose PO BID on Days 1–5, 15–19 • Methotrexate IT on Days 1 and 8 for CNS1/2 patients; on Day 1 for CNS3 patients • Methotrexate/Hydrocortisone/Cytarabine IT on Days 8, 15, 22 for CNS 3 patients
COG AALL1331 Block 2 (LR patients on Arms C-D, HR/IR patients on Arm A)	• Vincristine 1.5mg/m^2 (maximum 2 mg) IV on Day 1 • Dexamethasone 3 mg/m^2/dose PO BID on Days 1 –5 • Methotrexate 1000 mg/m^2 IV on Day 8 followed by leucovorin rescue • PEG-Asparaginase 2500 IU/m^2 IV on Day 9 or 10 • Cyclophosphamide 440 mg/m^2 daily on Days 15–19 • Etoposide 100mg/m^2 daily on Days 15–19 • Methotrexate IT on Day 8 for CNS1/2 patients • Methotrexate/Hydrocortisone/Cytarabine IT on Days 8, 22 for CNS3 patients
COG AALL1331 Block 3 (LR patients on Arm C, HR/IR patients on Arm A)	• Vincristine 1.5 mg/m^2 (maximum 2 mg) IV on Day 1 • Dexamethasone 3 mg/m^2/dose PO BID on Days 1 –5 • Cytarabine 3000 mg/m^2/dose every 12hours on Days 1, 2, 8, 9 • Erwinia L-Asparaginase 25,0000 IU/m^2 on Days 2, 4, 9, 11, 23 • Methotrexate 1000 mg/m^2 IV on Day 22 followed by leucovorin rescue • Methotrexate IT on Days 1, 22 for CNS1/2 patients; on Day 1 for CNS3 patients • Methotrexate/Hydrocortisone/Cytarabine IT on Day 22 for CNS3 patients

IV: intravenously; PO: orally; IT: intrathecally; BID: twice daily.

IT therapies dosed based on age and defined in the respective protocol.

Table 3.

L-Carnitine dosing.

Patient	Carnitine dosing	Carnitine timing
1	50mg/kg/d IV divided q8h then 100mg/kg/d IV divided q8h	Lower dose on Induction Day 23; higher dose on Induction Days 24–41 (19 d)
2	100mg/kg/d PO divided q8h	Induction Day 27 through Consolidation Day 29 (38 d) and Consolidation Days 40–56 (17 d)
3	45mg/kg/d IV divided q8h then PO at same dose	IV on Induction Day 33 through Consolidation Day 2 (19 d); PO from Consolidation Day 3 through end of Delayed Intensification (approximately 6 months)
4	50mg/kg/d IV divided q12h then PO at same dose	IV on Induction Days 22–26 (5 d); PO on Induction Day 27 through Consolidation Day 13 (22 d)
5	990 mg PO BID (18mg/kg/d)	First course given as prophylaxis on Induction Days 1–29 (30 d); future courses started the day of PEG-asparaginase administration and continued for 14 d each
6	85 mg/kg/d IV divided q8h then PO at same dose	IV on Induction Days 25–29 (5 d); PO on Induction Day 30 through Consolidation Day 22 (28 d); future courses given for 1 week before and 1 week after each dose of PEG-asparaginase

IV: intravenously; PO: orally; BID: twice daily.

Table 4.

Individual patient laboratory data.

	PEG-Asp	Total bilirubin						Transaminases (AST/ALT)		
Case #	Day given	Pre-Asp values	Day rise began	Peak values	Peak day	Day fall began	Day total Bili < 2	Pre-Asp values	Peak values	Peak day
1	4	0.8	22	24.3	26	28	*a*	188/314	6297/1918	45
2	4	1.0	14	10.2	25	26	46	26/117	108/257	24
3	4	0.6	15	42.4	31	39	60	26/21	146/216	31
4	3	0.2	15	6.7	22	23	43	21/12	214/688	23
5	4	2.5	1	4.0	7	8	9	43/50	135/92	0
6	4	0.4	15	17.3	25	26	55	41/23	144/303	20

AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Bilirubin values are in mg/dL. “Day” refers to protocol treatment day.

[a]Total bilirubin never fell below 2 mg/dL.