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Asparaginase

Updated: September 19, 2023.

OVERVIEW

Introduction

Asparaginase is a bacterial enzyme that is used as an antineoplastic agent, largely in the therapy of acute lymphocytic leukemia (ALL). Asparaginase has many side effects, one of which is hepatic injury that is characterized by inhibition of hepatic protein synthesis, marked cholestasis and steatosis, which is usually reversible but can be severe and lead to death from hepatic failure.

Background

Asparaginase (as par' a jin ase), often referred to as L-asparaginase, is a bacterial enzyme that acts to decrease tissue stores of asparagine, a secondary amino acid that is important in the growth of many cancers. Asparaginase, prepared from E. coli, was introduced into cancer chemotherapy over 50 years ago and remains an important agent in the therapy of acute lymphocytic leukemia. Asparaginase has activity against other cancer types but is rarely used for other indications. Asparaginase was first approved for use in the United States in 1972 as an anticancer agent, with initial preparations being prepared from E. coli. Pegylated formulations of E. coli-derived asparaginase (pegaspargase) became available and were approved for use in 1994 and are currently available under the brand name Oncaspar. Another form of pegylated asparaginase referred to as calaspargase pegol (brand name Asparlas) was approved in 2018 as therapy of ALL in children and young adults (ages 1 month to 21 years). These preparations can be given every two (pegaspargase) or three (calaspargase) weeks and have largely replaced standard asparaginase. Asparaginase made from other bacteria (Erwinia chrysanthemi) was approved for use in the United States in 2011 under the brand name Erwinaze, and a recombinant form was originally approved in 2021 under the brand name Rylaze. Standard asparaginase is given either by intramuscular injection or, more typically, intravenous injection in doses of 25,000 IU/m^2 three times weekly in 14-day cycles. Pegaspargase can also be given intramuscularly or intravenously, typically in a dose of 2500 IU/m^2 every two or three weeks. Both standard and pegylated asparaginase are usually given in combination with other antineoplastic agents such as vincristine, mercaptopurine, methotrexate, daunorubicin, and prednisone. Asparaginase has many dose related toxicities including nausea, fever, hypersensitivity reactions (urticaria, wheezing), clotting abnormalities, bone marrow suppression, pancreatitis, hepatotoxicity and central nervous system toxicities.

Hepatotoxicity

Some abnormalities of liver test results occur in almost all patients treated with either asparaginase or pegaspargase. Most typical is a decrease in serum albumin and clotting factors (including II, V, VII, VIII, IX, prothrombin and fibrinogen) due to inhibition of hepatic protein synthesis. Most patients also have a rise in

alkaline phosphatase levels and a lower proportion have increases in serum aminotransferase levels and bilirubin. Symptoms of fatigue and anorexia may be present. The inhibition of clotting factor and thrombolytic activity rarely results in excess bleeding, but paradoxically can also cause excessive clotting and a hypercoagulable state. Serum aminotransferase elevations during asparaginase therapy are mild-to-moderate in severity (2 to 10 times the upper limit of normal) and self-limiting. The abnormalities typically arise after 2 to 3 weeks of therapy and resolve within 2 to 4 weeks of stopping.

Asparaginase and pegasparase can also result in a more severe and protracted form of liver injury marked by fatigue, dark urine and jaundice arising 2 to 3 weeks after starting the enzyme infusions and often between courses of therapy. The hepatic dysfunction is accompanied by hepatic steatosis which can be severe and accompanied by jaundice, hepatomegaly and evidence of hepatic failure (somnolence, coma, ascites). Imaging of the liver shows hepatomegaly and marked fat accumulation arising within a few weeks of starting the agent and sometimes after a single dose. Autoimmune and immunoallergic features are uncommon. The course of illness varies. Recovery tends to be slow, jaundice resolving in 2 to 8 weeks and serum enzymes thereafter. Deaths due to asparaginase hepatotoxicity have been reported but are rare (Case 1). The frequency of this clinically apparent liver injury after asparginase therapy is estimated to be 15% to 20% in adults but less than 5% in children. Furthermore, the rate of severe hepatic injury from asparaginase has been less frequent in recent years, perhaps due to safer dosage regimens, more purified preparations of the bacterial enzyme, better monitoring and dose adjustments based upon better understanding of pharmacokinetics. Nevertheless, the frequency of hepatotoxicity appears to be similar with standard and pegylated forms of asparaginase. Risk factors for clinically apparent liver injury include higher doses, older age and preexisting obesity, hyperlipidemia and diabetes. Although of unproven benefit, therapy with L-carnitine and vitamin B is often recommended. Interestingly, in many instances asparaginase therapy is tolerated after recovery from the acute episode with either no or milder liver injury (Case 2). Switching from an E. coli to an Erwinia chrysanthemi-derived asparaginase may also be less likely to induce a recurrence of hepatic injury.

The clinical features of hepatic injury due to asparaginase can be overshadowed by its other systemic toxicities, including severe nausea and vomiting, weakness, edema, pancreatitis and encephalopathy. Although hypersensitivity reactions to asparaginase are common (it is a bacterial not a human enzyme), these usually occur early before the appearance of liver injury and the hepatic injury is rarely accompanied by fever or eosinophilia or autoantibody formation.

Likelihood score: A (well known cause of clinically apparent liver injury).

Mechanism of Liver Injury

Asparaginase is directly toxic to hepatocytes resulting in inhibition of protein synthesis and export of lipoproteins and lipids, with resultant steatosis and hepatic dysfunction. As with other forms of direct hepatotoxicity, the liver injury attributed to asparaginase arises rapidly, is dose related, and is rarely accompanied by with immunological features. The mechanism of the direct injury is not clear but may be the result of substrate depletion of asparagine or possibly arginine (as a consequence of argininase activity in the bacterial enzyme preparation). In animal models, asparaginase causes similar hepatic injury to that in humans. Hepatic injury with Erwinia-derived asparaginase may be less common than with E. coli-derived enzyme, but head-to-head comparisons have not been made.

Outcome and Management

Asparaginase is typically given in 14 or 28 day cycles while pegaspargase is given at two-week intervals, and consequently the hepatic injury may first become clinically apparent after the drug is stopped. Further use of asparaginase (with dose reduction) should be delayed until hepatic function has been restored. Patients receiving asparaginase should be monitored for hepatic function and the drug stopped or dose adjusted if liver test

abnormalities arise. Once clinically apparent liver injury arises, supportive clinical care and treatment of complications are essential. Anecdotal reports suggest that intravenous infusions of L-carnitine (50 mg/kg daily in divided doses for 5 to 8 days or until the injury resolves) and vitamin B preparations may be helpful. The efficacy of L-carnitine in ameliorating or preventing hepatic injury from asparaginase has not been shown in prospective controlled trials, but the approach appears to be safe and without serious adverse effects. In animal models, L-carnitine ameliorates the hepatic injury induced by asparaginase as do infusions of arginine.

Drug Class: Antineoplastic Agents

CASE REPORTS

Case 1. Severe hepatic injury and death due to asparaginase.(1)

A 68 year old man with acute lymphocytic leukemia was treated with induction chemotherapy using daunorubicin, vincristine, methotrexate, asparaginase, cyclophosphamide and prednisone. Mild liver test abnormalities were present even before therapy but rose precipitously between day 19 and 26 of therapy. Chemotherapy was stopped. Serum bilirubin was 10.9 mg/dL, ALT 122 U/L and alkaline phosphatase 480 U/L (Table). A liver biopsy showed diffuse microvesicular steatosis with minimal inflammation, necrosis or fibrosis. Several days later, he became progressively somnolent and was transferred to the intensive care unit. Serum ammonia levels were high (227 µmol/L; normal <35), but lactate and glucose levels were normal. He developed progressive coma, sepsis, renal failure and died 54 days after starting therapy and 4 weeks after stopping all chemotherapy.

Key Points

Medication:	Asparaginase (dose not given)
Pattern:	Cholestatic (R=0.7)
Severity:	5+ (jaundice, hepatic failure and death)
Latency:	26 days
Recovery:	None
Other medications:	Chemotherapy for leukemia included prednisone, daunorubicin, vincristine, methotrexate, and cyclophosphamide.

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
0	pre	50	159	2.4	Started chemotherapy
5 days		144	141	0.8	
11 days		182	110	1.0	
19 days		124	64	1.0	
26 days	0	122	480	10.9	Chemotherapy stopped
28 days	2 days	111	588	11.9	Liver biopsy
32 days	6 days	132	982	19.5	Somnolence
42 days	16 days	526	2735	20.9	Coma
50 days	24 days	184	2688	32.0	
54 days	28 days	Died of hepatic and multiorgan failure			

Table continued from previous page.

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Normal Values		**<38**	**<107**	**<1.2**	

Comment

While this patient was receiving 6 chemotherapeutic agents concurrently, the hepatic injury most closely resembled asparaginase hepatotoxicity, which typically arises after 2 to 3 weeks of therapy and is marked by gradual elevations in alkaline phosphatase to high levels with variable increases in serum bilirubin and aminotransferase levels. Some cases are severe and associated with hepatomegaly, fatty metamorphosis, severe hepatic dysfunction, progressive jaundice and hepatic coma. The condition can progress for several weeks after stopping therapy and rare fatal instances such as the current case have been described. Complicating factors in this case were age and possibly preexisting liver disease. Asparaginase toxicity is not idiosyncratic, but there appears to be variable susceptibility to the injury, and risk factors include dose, age, obesity and preexisting diabetes. Early in the course, the fatty metamorphosis may be largely microvesicular steatosis, whereas later, a mixed or fully macrovesicular steatosis may be present. Unlike the acute fatty liver with hepatic failure that occurs with Reye syndrome and mitochondrial injury due to nucleoside analogues, the steatosis and liver injury associated with asparaginase is less commonly associated with lactic acidosis, hyperammonemia and hypoglycemia, although it can be accompanied by pancreatitis. Unlike the fatty liver that occurs with alcoholic and nonalcoholic liver disease (NASH), there is little ballooning degeneration, Mallory bodies or sinusoidal fibrosis.

Case 2. Liver injury due to pegaspargase with recurrence on re-exposure.(2)

A 33 year old woman with acute lymphocytic leukemia was treated with induction chemotherapy using daunorubicin, vincristine, methotrexate, cytarabine, prednisone, and pegaspargase. Routine liver tests were normal before starting chemotherapy. Pegaspargase was given as a single intravenous infusion of 2520 IU on day 4. She developed symptoms of fatigue, weakness, nausea, and poor appetite a week after the pegaspargase infusion. Her symptoms persisted, and two weeks later she noted dark urine and jaundice and was found to have abnormal liver tests. Serum bilirubin was 8.4 mg/dL, ALT 1076 U/L and alkaline phosphatase 314 U/L (Table). Serum albumin was 1.5 g/dL and INR 1.1. All chemotherapy was stopped, and she was hospitalized. An abdominal ultrasound showed changes suggestive of hepatic steatosis but no evidence of biliary obstruction or gall stones. Tests for hepatitis A, B and C were negative. She had low levels of ANA (1:80), but SMA and AMA were negative, and immunoglobulin levels were normal. She was monitored on no therapy. Liver tests began to improve, and chemotherapy was restarted. A single infusion of pegaspargase was given and a few weeks later she again developed fatigue and dark urine and liver tests rose: bilirubin from 0.8 to 3.8 mg/dL, ALT from 47 to 533 U/L, and Alk P from 194 to 1018 U/L. Chemotherapy was held and liver tests improved once again. In follow up, chemotherapy was restarted with addition of mercaptopurine instead of pegaspargase. Eight months later she was in remission and all liver tests were normal.

Key Points

Medication:	Pegaspargase
Pattern:	Hepatocellular (R=14.5)
Severity:	3+ (jaundice, hospitalization)
Latency:	21 days
Recovery:	Recurrence with re-exposure, ultimate complete recovery 8 months later

Table continued from previous page.

Other medications:	Chemotherapy for leukemia included prednisone, daunorubicin, vincristine, methotrexate, and cytarabine.

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
0	pre	46	76	0.6	Started chemotherapy
4 days	-20 days				Pegaspargase given iv
9 days	-14 days	66	70	1.7	Onset of symptoms
23 days	0	1076	193	8.4	Hospitalization
26 days	3 days	2331	314	12.8	Ultrasound: steatosis
30 days	7 days	1112	420	3.0	Discharged
5 weeks	13 days	217	218	2.3	Chemotherapy restarted
	16 days	200	183	1.5	
7 weeks	4 weeks	57	126	1.3	Pegaspargase given iv
2 months	5 weeks	47	193	1.2	
	6 weeks	67	194	0.8	
	7 weeks	533	1018	3.8	Fatigue and dark urine
	7.5 weeks	294	780	1.6	
3 months	8 weeks	191	416	0.9	
	11 weeks	57	163	0.5	Mercaptopurine started
4 months	3 months	76	133	0.7	
	4 months	56	119	0.3	
9 months	8 months	37	92	0.6	In remission
Normal Values		**<50**	**<125**	**<1.2**	

Comment

This patient developed typical asparaginase hepatotoxicity starting within a week of starting chemotherapy and with peak levels of enzyme elevations and jaundice 3 weeks after the single infusion of pegaspargase. Also typical was the fall in serum protein levels and marked hepatic steatosis. A liver biopsy was not done but asparaginase hepatotoxicity was suspected. Once it was clear that she was recovering, chemotherapy was restarted, and she was given another infusion of pegaspargase. Two weeks later she was again symptomatic and jaundiced, this second episode being somewhat less severe than the first. Unlike with immunoallergic forms of idiopathic drug induced liver injury, rechallenge with asparaginase often causes a less severe recurrence and can be mild and subclinical. Because of the importance of asparaginase in treatment of acute leukemia, attempts are often made to restart the agent despite a severe episode of hepatotoxicity. Rechallenge with asparaginase should be done cautiously, perhaps with a lower dose or a different formulation (such as Erwinia chrysanthemi derived asparaginase).

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Asparaginase – Erwinaze®

Asparaginase (recombinant) – Rylaze®

Pegaspargase – Oncaspar®

DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING [Asparaginase]

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Asparaginase	9015-68-3	Large protein	Unavailable
Pegaspargase	130167-69-0	Large protein	Unavailable

CITED REFERENCES

1. Bodmer M, Sulz M, Stadlmann S, Droll A, Terracciano L, Krähenbühl S. Fatal liver failure in an adult patient with acute lymphoblastic leukemia following treatment with L-asparaginase. Digestion 2006; 74: 28-32. PubMed PMID: 16988508.
2. Kamal N, Koh C, Samala N, Fontana RJ, Stolz A, Durazo F, Hayashi PH, et al.; Drug-Induced Liver Injury Network. Asparaginase-induced hepatotoxicity: rapid development of cholestasis and hepatic steatosis. Hepatol Int. 2019;13:641-648. [Case #6] PubMed PMID: 31392570.

ANNOTATED BIBLIOGRAPHY

References updated: 20 July 2023

Abbreviations: ALL, acute lymphocytic leukemia.

Zimmerman HJ. Hepatotoxic effects of oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 673-708.

(Expert review of hepatotoxicity of neoplastic agents published in 1999; mentions high incidence of hepatic and pancreatic side effects from asparaginase, liver injury marked by steatosis which is found in 50-90% of patients and worsens with duration of treatment).

DeLeve L. L-asparaginase. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 557.

(Review of hepatotoxicity of anticancer drugs states that the rate of liver test abnormalities and clinically apparent liver injury due to asparaginase therapy is considerably lower in the recent literature, although severe cases are still reported).

Chabner BA, Bertino J, Clearly J, Ortiz T, Lane A, Supko JG, Ryan DP. Cytotoxic agents. Chemotherapy of neoplastic diseases. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1677-730.

(Textbook of pharmacology and therapeutics; mentions that the toxicity of asparaginase is due to its antigenicity and to its actions in inhibiting protein synthesis).

Haskell CM, Canellos GP, Leventhal BG, Carbone PP, Block JB, Serpick AA, Selawry OS. L-asparaginase: therapeutic and toxic effects in patients with neoplastic disease. N Engl J Med 1969; 281: 1028-34. PubMed PMID: 4898857.

(Early experience with asparaginase in 55 patients with cancer or leukemia, given iv for 3 weeks; common side effects were nausea, fever, hypersensitivity reactions, clotting abnormalities, pancreatitis and CNS toxicity; the most frequent side effect was liver dysfunction characterized by decreases in serum albumin and slight elevations in Alk P, ALT and bilirubin; in one instance liver injury was severe).

Gross MA, Speer RJ, Hill JM. Hepatic lipidosis associated with L-asparaginase treatment. Proc Soc Exp Biol Med 1969; 130: 733-6. PubMed PMID: 5773660.

(Study in mice given different doses of asparaginase with different degrees of purity; highest purity samples had little hepatotoxicity).

Pratt CB, Simone JV, Zee P, Aur RJ, Johnson WW. Comparison of daily versus weekly L-asparaginase for the treatment of childhood acute leukemia. J Pediatr 1970; 77: 474-83. PubMed PMID: 5278225.

(Comparison of daily versus weekly infusions of asparaginase in 19 children with acute leukemia; evidence of hepatotoxicity occurred in all patients with decrease in albumin in 68%, increase in AST in 63%, Alk P in 16%, bilirubin in 47%, liver changes found on autopsies were "vacuolization of hepatocytes").

Leventhal BG, Skeel RT, Yankee RA, Henderson ES. L-asparaginase (NSC- 09229) plus azaserine (NSC-742) in acute lymphatic leukemia. Cancer Chemother Rep 1970; 54: 47-51. PubMed PMID: 4945997.

(Result of use of asparaginase and azaserine in 27 children with acute lymphocytic leukemia; hypersensitivity reactions occurred in 33%, Alk P elevations in 77%, decreases in albumin in 59%, clotting abnormalities in 88%).

Oettgen HF, Stephenson PA, Schwartz MK, Leeper RD, Tallai L, Tan CC, Clarkson BD, et al. Toxicity of E. coli L-asparaginase in man. Cancer 1970; 25: 253-78. PubMed PMID: 4905153.

(Analysis of toxicity of asparaginase in 131 children and 143 adults with neoplastic disease; elevations in Alk P occurred in 31-47% of patients, AST in 46-63%, bilirubin in 29-51%, and decreases in albumin in 71-82%, usually arising during the 2nd to 3rd week of therapy and resolving upon stopping; fatty metamorphosis found in 73% of autopsies).

Bernard J, Jacquillat C, Boiron M, Weil M, Bussel A, Larrieu MJ, Delobel J, et al. [Treatment of acute leukemia with the L-asparaginase. Preliminary results based on 84 cases]. Presse Med. 1970; 78: 161-6. French.

(Analysis of results of treating 75 patients with acute leukemia with asparaginase; liver toxicity was frequent and marked by falls in serum albumin and cholesterol with rises in Alk P, while ALT elevations were rare; two patients developed hepatic insufficiency which may have contributed to their deaths).

Burchenal JH. A summary of the clinical status of asparaginase. Recent Results Cancer Res 1970; 33: 350-4. PubMed PMID: 5292724.

(Summary of a workshop on asparaginase).

Jacquillat C, Weil M, Bussel A, Loisel JP, Rouesse T, Larrieu MJ, Boiron M, et al. Treatment of acute leukemia with L-asparaginase--preliminary results on 84 cases. Recent Results Cancer Res 1970; 33: 263-78. PubMed PMID: 5292720.

(Among 84 patients with acute leukemia given asparaginase, early toxicities included hypersensitivity reactions [fever, urticaria and anaphylaxis], and late toxicities where often hepatic with weight loss and elevations in bilirubin, Alk P [50%] and ALT [36%], with decrease in albumin [60%], cholesterol [72%] and fibrinogen, usually arising after the first week of therapy and beginning to resolve within a week of stopping).

Marmont AM, Damasio EE. Some clinical observations on the treatment with L-asparaginase of the acute leukemias. Recent Results Cancer Res 1970; 33: 296-315. PubMed PMID: 4949165.

(Discussion of side effects of asparaginase: "there can be no doubt that L-ase profoundly affects the liver cell").

Carbone PP, Haskell CM, Leventhal BG, Block JB, Selawry OS. Clinical experience with L-asparaginase. Recent Results Cancer Res 1970; 33: 236-43. PubMed PMID: 4949163.

(Summary of results using asparaginase, similar to report by Haskell [1969]).

Zubrod CG. The clinical toxicities of L-asparaginase in treatment of leukemia and lymphoma. Pediatrics 1970; 45: 555-9. PubMed PMID: 5438160.

(Review of toxicities of asparaginase, hepatic abnormalities being the most common).

Beard ME, Crowther D, Galton DA, Guyer RJ, Fairley GH, Kay HE, Knapton PJ, et al. L-asparaginase in treatment of acute leukaemia and lymphosarcoma. Br Med J 1970; 1 (5690): 191-5. PubMed PMID: 4904933.

(Among 40 patients treated with L-asparaginase, nausea and vomiting were common as were "slight abnormalities in liver function tests").

Pratt CB, Johnson WW. Duration and severity of fatty metamorphosis of the liver following L-asparaginase therapy. Cancer 1971; 28: 361-4. PubMed PMID: 5109448.

(Analysis of liver histology from autopsies in 31 children after asparaginase therapy, 27 [87%] had fatty metamorphosis for periods of up to 261 days after last dose, severity decreasing 60 days after dosing, but fatty change also found in 51% of children with leukemia who did not receive asparaginase).

Biggs JC, Chesterman CN, Holliday J. L-asparaginase--clinical experience in leukaemia, lymphoma and carcinoma. Aust N Z J Med 1971; 1: 1-7. PubMed PMID: 4934741.

(Among 11 patients with leukemia or cancer treated with asparaginase, mild elevations in ALT and Alk P [2-4 times ULN] occurred in 4).

Revol L, Fière D, Guyon JM. [Accidents due to asparaginase]. J Med Lyon 1971; 52: 831-3. French. PubMed PMID: 5136251.

Oberling F, Cazenave JP, Lang JM, Kurtz D, Mayer G, Waitz R. [Apropos of certain toxic effects of L-asparaginase in human therapy]. Sem Hop 1971; 47: 1421-5. French. PubMed PMID: 4326093.

Land VJ, Sutow WW, Fernbach DJ, Lane DM, Williams TE. Toxicity of L-asparginase in children with advanced leukemia. Cancer 1972; 30: 339-47. PubMed PMID: 4626307.

(Among 105 patients with leukemia treated with asparaginase, liver test abnormalities occurred in most patients and were fatal in two [fatty liver]).

Hasegawa Y, Suzuki T, Motegi F, Takanashi R. [Severe toxicity of L-asparaginase in the treatment of acute leukemia--the hepatocerebral lesions (author's transl)]. Rinsho Ketsueki 1973; 14: 917-24. Japanese. PubMed PMID: 4519904.

Haghbin M, Tan CC, Clarkson BD, Miké V, Burchenal JH, Murphy ML. Intensive chemotherapy in children with acute lymphoblastic leukemia (L-2 protocol). Cancer 1974; 33: 1491-8. PubMed PMID: 4526012.

(Experience in treating 75 children with leukemia with intensive chemotherapy including asparaginase; two died of serum hepatitis from platelet transfusions; hepatotoxicity not discussed).

Rutter DA. Letter: Toxicity of asparaginases. Lancet 1975; 1 (7919): 1293-4.

(Retrospective review of 77 courses of either E. coli or Erwinia carotovora derived asparaginase in patients with acute leukemia seen at 3 London hospitals, found slightly higher rates of side effects with E. coli product [liver injury not mentioned]; 10 patients with hypersensitivity reactions to one tolerated the other).

Olive D, Cartault F, Legras B, Neimann N. [Evaluation in children of the clinical, biological and electroencephalographic side effects of L-asparaginase]. Pediatrie 1976; 31: 259-78. French. PubMed PMID: 1069234.

Woods WG, O'Leary M, Nesbit ME. Life-threatening neuropathy and hepatotoxicity in infants during induction therapy for acute lymphoblastic leukemia. J Pediatr 1981; 98: 642-5. PubMed PMID: 6937637.

(Two children [ages 16 and 14 months] developed neuropathy and hepatic failure during 4th week of chemotherapy with regimens including asparaginase for acute lymphocytic leukemia, with liver biopsies showing fat, focal necrosis and mild inflammation, one survived and one died of hepatic failure).

Haskell CM. L-Asparaginase: human toxicology and single agent activity in nonleukemic neoplasms. Cancer Treat Rep 1981; 65 Suppl 4 : 57-9.

(Unlike other antineoplastic agents, asparaginase has little bone marrow toxicity and its main side effects are on liver, kidneys, pancreas, central nervous and clotting system; hypersensitivity reactions can also occur and can be severe).

Cairo MS. Adverse reactions of L-asparaginase. Am J Pediatr Hematol Oncol 1982 Fall; 4: 335-9. PubMed PMID: 6959544.

(Review of toxicity of asparaginase; hepatic injury is most common and is marked by changes in AST, Alk P, bilirubin and albumin).

Distasio JA, Salazar AM, Nadji M, Durden DL. Glutaminase-free asparaginase from vibrio succinogenes: an antilymphoma enzyme lacking hepatotoxicity. Int J Cancer 1982; 30: 343-7. PubMed PMID: 6752048.

(Unlike standard, E coli-derived asparaginase, a glutaminase-free preparation did not cause hepatotoxicity or fatty liver in mice, suggesting that the hepatotoxicity of asparaginase is due to a contaminant).

Durden DL, Salazar AM, Distasio JA. Kinetic analysis of hepatotoxicity associated with antineoplastic asparaginases. Cancer Res 1983; 43: 1602-5. PubMed PMID: 6339039.

(Comparison of glutaminase-free and standard asparaginase in a mouse model found little hepatotoxicity, even with 3-4 weeks of therapy).

Kafkewitz D, Bendich A. Enzyme-induced asparagine and glutamine depletion and immune system function. Am J Clin Nutr 1983; 37: 1025-30. PubMed PMID: 6342356.

(Induced immune deficiency in mice given E. coli derived asparaginase was associated with decrease in glutamine, which did not occur with V. succinogenes derived product that is free of glutaminase).

Jenkins R, Perlin E. Severe hepatotoxicity from Escherichia coli L-asparaginase. J Natl Med Assoc 1987; 79: 775, 779.

(51 year old woman with diabetes and acute lymphocytic leukemia developed jaundice at the end of a 10 day course of asparaginase [bilirubin 9.0 rising to 25.5 mg/dL, AST 344 to 1920 U/L, Alk P 400 to 1650 U/L, with high ammonia and decreased fibrinogen], but gradually improved and all tests were normal 4 months later).

Bessho F, Kinumaki H, Yokota S, Hayashi Y, Kobayashi M, Kamoshita S. Liver function studies in children with acute lymphocytic leukemia after cessation of therapy. Med Pediatr Oncol 1994; 23: 111-5. PubMed PMID: 8202032.

(Among 27 children with acute leukemia, serum ALT levels were often elevated during induction and maintenance therapy but were normal or near normal in all 3 months after stopping therapy and remained normal in long term follow up).

Wróbel G, Dobaczewski G, Kazanowska B, Boguslawska-Jaworska J, Balwierz W, Balcerska A, Bubala H, et al. [Adverse reactions associated with the use of L-asparaginase during therapy of patients with B non-

Hodgkin's lymphoma. Report of the Polish Paediatric Leukaemia/Lymphoma Study Group]. Med Wieku Rozwoj 2000; 4: 67-72. Polish.

(Abstract: among 66 children with non- Hodgkin lymphoma treated with asparaginase, 20 [30%] developed adverse reactions, mostly typically coagulation abnormalities [18%] and "impairment of liver function" [9%]).

Sahoo S, Hart J. Histopathological features of L-asparaginase-induced liver disease. Semin Liver Dis 2003; 23: 295-9. PubMed PMID: 14523682.

(Four patients developed hepatomegaly and abnormal liver tests 2-20 days after starting asparaginase [bilirubin 1.6-39.0 mg/dL, ALT 69-3916 U/L, Alk P 118-1075 U/L, albumin 2.2-2.6 g/dL] and had diffuse macro- and micro-vesicular steatosis on liver biopsy; one patient had acute liver failure and died).

Graham ML. Pegaspargase: a review of clinical studies. Adv Drug Deliv Rev 2003; 55: 1293-302. PubMed PMID: 14499708.

(Review of clinical trials of pegylated asparaginase; toxicities were similar to the standard product and included hypoalbuminemia, lipoprotein abnormalities and elevations in ALT, Alk P and bilirubin).

Bodmer M, Sulz M, Stadlmann S, Droll A, Terracciano L, Krähenbühl S. Fatal liver failure in an adult patient with acute lymphoblastic leukemia following treatment with L-asparaginase. Digestion 2006; 74: 28-32. PubMed PMID: 16988508.

(68 year old man developed jaundice after 26 days of chemotherapy which included asparaginase [bilirubin 10.9 rising to 32.2 mg/dL, ALT 122 rising to 526 U/L, Alk P 480 rising to 2688 U/L], with progressive somnolence, hyperammonemia, coagulopathy, coma and death from liver failure 4 weeks later: Case 1).

Flores-Calderón J, Exiga-Gonzaléz E, Morán-Villota S, Martín-Trejo J, Yamamoto-Nagano A. Acute pancreatitis in children with acute lymphoblastic leukemia treated with L-asparaginase. J Pediatr Hematol Oncol 2009; 31: 790-3. PubMed PMID: 19770681.

(Among 266 children given chemotherapy [including asparaginase with prednisone, vincristine, daunorubicin and methotrexate] for acute lymphocytic leukemia over a 6 year period, 18 [7%] developed pancreatitis arising 1-18 days after last dose of asparaginase [amylase 19-2893 U/L]; no fatalities, but 3 developed a pseudocyst and chronic symptoms and 3 required long term insulin).

Yong W, Zheng W, Zhu J, Zhang Y, Wang X, Xie Y, Lin N, et al. L-asparaginase in the treatment of refractory and relapsed extranodal NK/T-cell lymphoma, nasal type. Ann Hematol 2009; 88: 647-52. PubMed PMID: 19107482.

(Among 45 adult patients receiving asparaginase for refractory and relapsed NKT cell leukemia, side effects included elevations in ALT in 51%, bilirubin in 33% and decreases in albumin in 9%).

Ladas EJ, Kroll DJ, Oberlies NH, Cheng B, Ndao DH, Rheingold SR, Kelly KM. A randomized, controlled, double-blind, pilot study of milk thistle for the treatment of hepatotoxicity in childhood acute lymphoblastic leukemia (ALL). Cancer 2010; 116: 506-13. PubMed PMID: 20014183.

(Among 50 children with acute leukemia given maintenance chemotherapy [vincristine, mercaptopurine, methotrexate and prednisone] who had ALT elevations and who were treated with either milk thistle or placebo, there were few differences in subsequent ALT, AST and bilirubin levels, and elevations of serum ALT or AST above 5 times ULN occurred equally with or without milk thistle).

Raetz EA, Salzer WL. Tolerability and efficacy of L-asparaginase therapy in pediatric patients with acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2010; 32: 554-63. PubMed PMID: 20724951.

(Review of safety and efficacy of asparaginase in children with ALL discusses hypersensitivity reactions and toxicity caused by inhibition of protein synthesis, which includes pancreatitis, thrombosis, and liver dysfunction, some

degree of which occurs in most patients, with hepatic steatosis in 87% which often persists for months after discontinuation).

Tsutsui M, Koike M, Komatsu N. [Fulminant hepatitis possibly caused by L-asparaginase during induction chemotherapy in a patient with acute lymphoblastic leukemia]. Rinsho Ketsueki. 2012; 53: 531-4. Japanese. PubMed PMID: 22728556.

(44 year old man with ALL developed abnormal liver tests 10 days after starting asparaginase with progressive injury and death by day 32).

Okamura A, Nishimura M, Sanada Y, Yakushijin K, Matsuoka H, Yamamoto K, Minami H. L-Asparaginase-induced fulminating liver dysfunction. Int J Hematol 2013; 98: 6-7. PubMed PMID: 23702916.

(49 year old woman with ALL developed liver test abnormalities 20 days after starting therapy with CHOP and 5 doses of asparaginase [bilirubin 2.2 mg/dL, ALT 43 U/L, Alk P not given], with hepatomegaly and marked fatty liver by CT scan; recovery by day 100).

Roesmann A, Afify M, Panse J, Eisert A, Steitz J, Tolba RH. L-carnitine ameliorates L-asparaginase-induced acute liver toxicity in steatotic rat livers. Chemotherapy 2013; 59: 167-75. PubMed PMID: 24192517.

(Pretreatment with L-carnitine decreased the liver injury and steatosis of isolated perfused rat livers exposed to asparaginase).

Vetro C, Giulietti G, Calafiore V, Romano A, Di Raimondo F. A snapshot of asparaginase-induced liver insufficiency. Eur J Haematol 2014; 92: 271-2. PubMed PMID: 24329712.

(39 year old man with ALL and renal transplant developed hepatomegaly and marked fatty liver [by CT scan] 25 days after starting pegaspargase [bilirubin not given; AST 90 U/L, Alk P 167 U/L, albumin 2.3 g/dL, fibrinogen 0, antithrombin III 19%], with progressive liver failure and death).

Al-Nawakil C, Willems L, Mauprivez C, Laffy B, Benm'rad M, Tamburini J, Fontaine H, et al. Successful treatment of l-asparaginase-induced severe acute hepatotoxicity using mitochondrial cofactors. Leuk Lymphoma 2014; 55: 1670-4. PubMed PMID: 24090500.

(Three patients, ages 51 to 64 years, developed severe liver injury 11-22 days after starting asparaginase therapy for ALL [peak bilirubin 6.1-50.4 mg/dL, ALT 480-1150 U/L, Alk P 550-2400 U/L, CT scan showing hepatomegaly and fatty liver], all 3 recovering after L-carnitine and vitamin B therapy).

Saison J, Berger F, Lebosse F, Audoual R, Thomas X, Michallet M. Hepatomegaly and fever at the time of neutrophil recovery revealing L-asparaginase toxicity in the treatment of acute lymphoblastic leukemia. Am J Case Rep 2014; 15: 13-7. PubMed PMID: 24454976.

(52 year old man with ALL developed fever and hepatomegaly by day 25 of chemotherapy and, after 5 injections of asparaginase [bilirubin 7.5 mg/dL, ALT 148 U/L, Alk P 148 U/L], rising for 2 weeks and then returning to normal within 2 months, biopsy showing marked steatosis and mild necrosis).

Douer D, Aldoss I, Lunning MA, Burke PW, Ramezani L, Mark L, Vrona J, et al. Pharmacokinetics-based integration of multiple doses of intravenous pegaspargase in a pediatric regimen for adults with newly diagnosed acute lymphoblastic leukemia. J Clin Oncol 2014; 32: 905-11. PubMed PMID: 24516026.

(Among 51 adults with ALL treated with 192 doses of intravenous pegaspargase, ALT or AST elevations occurred in all patients [above 5 times ULN in 63%], and bilirubin in 26 patients [above 3 times ULN in 31%], but all resolved spontaneously [within 6-83 days], although therapy was delayed in 10 patients for high bilirubin and 11 for ALT or AST elevations).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America: an analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, none were attributed to asparaginase or pegaspargase).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 49 cases [5%] were attributed to antineoplastic agents including 2 to asparaginase and 2 to pegaspargase, all 4 of which were jaundiced, but none were fatal).

Horvat TZ, Pecoraro JJ, Daley RJ, Buie LW, King AC, Rampal RK, Tallman MS, et al. The use of Erwinia asparaginase for adult patients with acute lymphoblastic leukemia after pegaspargase intolerance. Leuk Res 2016; 50: 17-20. PubMed PMID: 27631159.

(Ten adults with ALL with hypersensitivity or intolerance of pegaspargase were able to tolerate Erwinia asparaginase without hypersensitivity reactions and with only mild-to-moderate hepatotoxicity).

Göpel W, Schnetzke U, Hochhaus A, Scholl S. Functional acute liver failure after treatment with pegylated asparaginase in a patient with acute lymphoblastic leukemia: potential impact of plasmapheresis. Ann Hematol 2016; 95: 1899-901. PubMed PMID: 27488287.

(44 year old man with ALL developed liver failure 3 days after receiving pegaspargase [bilirubin rising to ~29 mg/dL, ALTto 2.5 times ULN, GGT to 16 times ULN], recovering over 3 week period following plasmapheresis).

Alshiekh-Nasany R, Douer D. L-Carnitine for treatment of pegasparaginase-induced hepatotoxicity. Acta Haematol 2016; 135: 208-10. PubMed PMID: 26841296.

(56 year old man with ALL developed jaundice after a single infusion of pegaspargase [peak bilirubin 26.6 mg/dL, ALT ~230 U/L, Alk P not given], resolving after a 6 day course of L-carnitine).

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

(Review of the mechanism of action of asparaginase and its toxicity in children).

Toksvang LN, De Pietri S, Nielsen SN, Nersting J, Albertsen BK, Wehner PS, Rosthøj S, et al. Hepatic sinusoidal obstruction syndrome during maintenance therapy of childhood acute lymphoblastic leukemia is associated with continuous asparaginase therapy and mercaptopurine metabolites. Pediatr Blood Cancer 2017; 64. e26519.

(Among 130 children with ALL receiving a complex chemotherapy regimen that included 8-15 biweekly pegaspargase infusions, 29 developed liver injury diagnosed as sinusoidal obstruction syndrome [SOS] by clinical criteria alone, possibly due to asparaginase effects on mercaptopurine metabolism, but all children recovered).

Liu Y, Fernandez CA, Smith C, Yang W, Cheng C, Panetta JC, Kornegay N, et al. Genome-wide study links PNPLA3 variant with elevated hepatic transaminase after acute lymphoblastic leukemia therapy. Clin Pharmacol Ther 2017; 102: 131-40. PubMed PMID: 28090653.

(Testing of two cohorts of patients receiving asparaginase found associations of posttreatment ALT levels and the PNPLA3 variant that has been linked to ALT elevations in the general population and with alcoholic and nonalcoholic fatty liver disease).

Özdemir ZC, Turhan AB, Eren M, Bor Ö. Is N-acetylcysteine infusion an effective treatment option in L-asparaginase associated hepatotoxicity? Blood Res 2017; 52: 69-71. PubMed PMID: 28401107.

(2 year old with ALL developed liver test abnormalities after a fifth infusion of an E. coli derived asparaginase [bilirubin 7 mg/dL, ALT 501 U/L, Alk P 246 U/L, GGT 1297 U/L], with recovery after 6 days of N-acetylcysteine infusions and minimal hepatotoxicity with later chemotherapy using Erwinia asparaginase).

Blackman A, Boutin A, Shimanovsky A, Baker WJ, Forcello N. Levocarnitine and vitamin B complex for the treatment of pegaspargase-induced hepatotoxicity: A case report and review of the literature. J Oncol Pharm Pract 2018; 24: 393-7. PubMed PMID: 28523950.

(36 year old woman with ALL developed jaundice 4 days after a second dose of pegaspargase [days 4 and 17 of therapy] [bilirubin 11.5 mg/dL, ALT 2493 U/L, Alk P 270 U/L, INR 1.0], improving rapidly with L-carnitine [50 mg/k/day for 8 days] and vitamin B therapy and tolerating a reduced dose of pegaspargase, and resumption of chemotherapy with recurrence of liver injury 6 weeks later).

Burke PW, Aldoss I, Lunning MA, Devlin SM, Tallman MS, Pullarkat V, Mohrbacher AM, et al. Pegaspargase-related high-grade hepatotoxicity in a pediatric-inspired adult acute lymphoblastic leukemia regimen does not predict recurrent hepatotoxicity with subsequent doses. Leuk Res. 2018;66:49-56. PubMed PMID: 29407583.

(Among 51 adults with ALL treated with pegaspargase, 16 developed "high grade" hyperbilirubinemia and aminotransferase elevations, usually after the first dose, of whom 11 received another course of pegaspargase only 7 of whom had recurrence and none of whom died of hepatic failure).

Schulte RR, Madiwale MV, Flower A, Hochberg J, Burke MJ, McNeer JL, DuVall A, et al. Levocarnitine for asparaginase-induced hepatic injury: a multi-institutional case series and review of the literature. Leuk Lymphoma. 2018;59:2360-2368. PubMed PMID: 29431566.

(Among 6 children and young adults with ALL who developed liver injury with jaundice after chemotherapy with pegaspargase who were then treated with levocarnitine, the liver injury resolved in 5 but progressed to end-stage liver disease, pancreatitis and death in one).

Arora S, Klair J, Bellizzi AM, Tanaka T. L-carnitine and vitamin B complex for peg-L-asparaginase-induced hepatotoxicity. ACG Case Rep J. 2019;6:e00194. PubMed PMID: 31737724.

(A 58 year old woman with ALL developed evidence of liver injury 12 days after starting chemotherapy which included pegaspargase, and she was treated with levocarnitine with subsequent peak laboratory values of bilirubin 12.7 mg/dL, ALT 276 U/L and Alk P 1053 U/L, with ultimate complete resolution after which she tolerated chemotherapy using non-pegylated asparaginase).

Kamal N, Koh C, Samala N, Fontana RJ, Stolz A, Durazo F, Hayashi PH, et al.; Drug-Induced Liver Injury Network. Asparaginase-induced hepatotoxicity: rapid development of cholestasis and hepatic steatosis. Hepatol Int. 2019;13:641-648. PubMed PMID: 31392570.

(Among 1321 cases of confirmed drug induced liver injury enrolled in a U.S. prospective database between 2004 and 2017, 60 were due to cancer chemotherapeutic agents including 8 due to asparaginase [n=1] or pegaspargase [n=7], arising 9-21 days after starting therapy with initial and peak values of bilirubin 4.4 and 17.5 mg/dL, ALT 284 and 595 U/L, Alk P 159 and 785 U/L, all with low serum albumin levels [less than 2.0 g/dL], fatty liver by imaging, and ultimate complete resolution, one patient having similar but slightly milder injury upon re-exposure to pegaspargase).

Meunier L, Larrey D. Chemotherapy-associated steatohepatitis. Ann Hepatol. 2020;19:597-601. PubMed PMID: 32061473.

(Review of drug induced liver injury associated with steatosis or steatohepatitis including methotrexate, 5-fluorouracil, irinotecan, tamoxifen, and L-asparaginase which may be due to mitochondrial injury and can lead to chronic steatosis and cell injury).

Li RJ, Jin R, Liu C, Cao X, Manning ML, Di XM, Przepiorka D, et al. FDA approval summary: calaspargase pegol-mknl for treatment of acute lymphoblastic leukemia in children and young adults. Clin Cancer Res. 2020;26:328-331. PubMed PMID: 31444252.

(Summary of data on pharmacokinetics and safety that led to the FDA approval of calaspargase pegol as therapy of ALL in children and young adults [ages 1 month to 21 years] found that calaspargase and pegaspargase had similar patterns and rates of adverse events including ALT elevations above 5 times ULN in 52% vs 66%).

Lew G. Space for calaspargase? a new asparaginase for acute lymphoblastic leukemia. Clin Cancer Res. 2020;26:325-327. PubMed PMID: 31641006.

(Editorial in response to Li et al [2020] mentions that calaspargase has a longer half-life than standard pegaspargase and can be given every 3 weeks, but side effects and efficacy seem to be the same, and the role of calaspargase remains uncertain in the complicated regimens used to treat ALL in children).

Vrooman LM, Blonquist TM, Stevenson KE, Supko JG, Hunt SK, Cronholm SM, Koch V, et al. Efficacy and toxicity of pegaspargase and calaspargase pegol in childhood acute lymphoblastic leukemia: results of DFCI 11-001. J Clin Oncol. 2021;39:3496-3505. PubMed PMID: 34228505.

(Among 239 children or young adults [ages 1 month to 21 years] with ALL treated with calaspargase pegol every 3 weeks and pegaspargase every 2 weeks [2,500 IU/m^2per dose] for 30 weeks, drug levels were similar as were rates of response [complete response in 95% vs 99%] and adverse events including hypersensitivity reactions and pancreatitis; no specific mention of ALT levels or hepatotoxicity].

Schulte R, Hinson A, Huynh V, Breese EH, Pierro J, Rotz S, Mixon BA, et al. Levocarnitine for pegaspargase-induced hepatotoxicity in older children and young adults with acute lymphoblastic leukemia. Cancer Med. 2021;10:7551-7560. PubMed PMID: 34528411.

(Comparison of cohorts of pegaspargase treated patients with ALL who did [n=29] or did not [n=109] receive prophylaxis with levocarnitine in variable doses and routes of administration, demonstrated similar rates of hepatotoxicity with or without prophylaxis [14% vs 16%], although post-hoc adjustment for risk factors suggested a protective effect of levocarnitine).

Lee C, Leventhal TM, Anugwom CM. L-Asparaginase-induced hepatotoxicity treated successfully with L-carnitine and vitamin B infusion. Cureus. 2021;13:e16917. PubMed PMID: 34513489.

(69 year old woman with ALL developed evidence of liver injury and pancreatitis after receiving pegaspargase [bilirubin 2.0 rising to 7.6 mg/dL, ALT 72 to 142 U/L, Alk P 282 to 1170 U/L], with fatty liver by ultrasound and liver biopsy showing steatosis and canalicular cholestasis, with ultimate resolution having received a course of levocarnitine and vitamin B complex).

Defina M, Lazzarotto D, Guolo F, Minetto P, Fracchiolla NS, Giglio F, Forghieri F, et al. Levocarnitine supplementation for asparaginase-induced hepatotoxicity in adult acute lymphoblastic leukemia patients: A multicenter observational study of the campus all group. Leuk Res. 2022;122:106963. PubMed PMID: 36155352.

(Among 38 adults with ALL who developed asparaginase induced liver injury [33 with pegaspargase], onset was with the first course in 89% with a median latency of 11 [range 0 to 30] days and all received L-carnitine at a median of 2 [range 0 to 51] days after onset, resolving in a median of 14 [range 5 to 58] days, data that are similar to the literature on untreated asparaginase hepatotoxicity).

Wu S, Wang M, Alqahtani A, Lou M, Stock W, Bhojwani D, Alachkar H. Hispanic ethnicity and the rs4880 variant in SOD2 are associated with elevated liver enzymes and bilirubin levels in children receiving asparaginase-containing chemotherapy for acute lymphoblastic leukemia. Biomed Pharmacother. 2022;150:113000. PubMed PMID: 35658244.

(Among 143 children with ALL treated with asparaginase, hepatoxicity arose in 47% of Hispanic vs 33% of non-Hispanics, the Hispanic children being more likely to be overweight or obese [53% vs 44%] and more likely to have the CC genotype of rs4880 SNP of superoxide dismutase 2 [SOD2: 43% vs 15%]; in multivariate analysis, only Hispanic ethnicity was a significant risk factor for asparaginase hepatotoxicity).

Vetro C, Duminuco A, Gozzo L, Maugeri C, Parisi M, Brancati S, Longo L, et al. Pegylated asparaginase-induced liver injury: a case-based review and data from pharmacovigilance. J Clin Pharmacol. 2022;62: 1142-1150. PubMed PMID: 35342960.

(59 year old woman with ALL developed pancreatitis within a week of starting chemotherapy which included pegaspargase and which was followed by jaundice and progressive liver failure, lactic acidosis and death 37 days after starting chemotherapy).