How I treat the toxicities of pegasparaginase in adults with acute lymphoblastic leukemia

Ibrahim Aldoss[1] and Dan Douer[2]

[1]Gehr Family Center for Leukemia Research, Department of Hematology and Hematopoietic Cell Transplantation, City of Hope Medical Center, Duarte, CA; and [2]Jane Anne Nohl Division of Hematology, University of Southern California, Los Angeles, CA

Administering asparaginase has always been problematic in adults because most general oncologists who treat adults are not familiar with its usage and toxicity. The toxicity profile of the drug is unique and is not observed with any other chemotherapy agent. Furthermore, asparaginase is almost exclusively used in acute lymphoblastic leukemia (ALL), which is a very rare cancer in adults. Currently, the long-acting pegylated form (pegasparaginase) is the only *Escherichia coli*–derived asparaginase available in the United States. The use of pediatric regimens is likely to lead to more adult patients receiving multiple doses of pegasparaginase. However, oncologists who treat adults may be reluctant to use pegasparaginase or may unnecessarily discontinue administering it because of certain adverse effects. As a result, the clinical benefit of multiple doses of pegasparaginase will be missed. Despite the fact that pegasparaginase is associated with unique toxicities, the majority are nonfatal, manageable, and reversible. Here, we describe real-life cases of adults with ALL who were treated with pediatric-inspired regimens that incorporated pegasparaginase to illustrate the management of several pegasparaginase-associated adverse effects and guide whether and how to continue the drug. (*Blood*. 2020;135(13):987-995)

Introduction

Acute lymphoblastic leukemia (ALL) in adults is associated with inferior survival outcomes when compared with ALL in children, which is primarily because of the considerable risk of relapse in adults.[1-6] Although increased risk of relapse is partly related to the finding that adults more frequently develop ALL with unfavorable genetics,[7] it is also attributed to inadequate chemotherapeutic regimens historically used to treat adults.

Retrospective comparisons of adolescents and young adults with ALL have consistently demonstrated significantly longer survival for patients who are treated by pediatricians with a pediatric regimen than patients of the same age treated by oncologists who treat adults using adult regimens.[8-11] This prompted extension of pediatric or pediatric-inspired regimens to adults with ALL, with upper ages ranging from 39 to 60 years.[12-18] These studies have confirmed the feasibility and safety of administering such regimens to adults with ALL and have improved outcomes compared with historical adult regimens.[12-18] A key element of pediatric regimens for ALL is incorporation of multiple doses of postremission asparaginase, a bacterial enzyme that hydrolyses serum asparagine into aspartic acid and ammonia, thus depleting serum asparagine and depriving ALL cells of this nutrient.

Several randomized pediatric studies reported the favorable impact of intensive postremission asparaginase on leukemia outcomes.[19-21] For example, the Dana-Farber Consortium 77-01 study reported that patients treated with intensive postremission high-dose asparaginase had significantly superior outcomes compared with patients who did not receive postremission asparaginase.[19] Likewise, the POG 8704 study in T-cell ALL reported an improved 4-year continuous complete remission (CR) rate for patients randomly assigned to postremission high-dose asparaginase vs no asparaginase consolidation (68% vs 55%).[21] The CCG 1882 study reported superior event-free survival in high-risk children who received 5 cycles of postremission asparaginase compared with those who received 1 cycle (75% vs 55%).[20] Because of the success of adding asparaginase to pediatric regimens for ALL, recent prospective adult studies have incorporated more doses of asparaginase compared with historical adult regimens (6 to 15 vs 0 to 2 cycles).[12,14,22-26] Administering asparaginase can be problematic in adults because general oncologists who treat adults may not be familiar with its usage and toxicity. The toxicity profile of asparaginase, summarized in Table 1, is unique and is not observed with other chemotherapy agents. Furthermore, asparaginase is almost exclusively used in ALL, which is a rare cancer in adults.

In the United States, the long-acting pegylated form (pegasparaginase) is the only available *Escherichia coli*–derived asparaginase. Our standard dose of pegasparaginase is 2000 IU/m² for adults up to age 55 years compared with 2500 IU/m² used in children because this dose seems to be safer, with adequate pharmacokinetic and pharmacodynamic properties.[25-28] Of note, other groups used a lower pegasparaginase dose (1000 IU/m²) to reduce toxicities while maintaining adequate activity,[24,29] with

Table 1. The rate and risk factors for pegasparaginase toxicities in adults

Toxicity	Any grade (%)	High grade (≥ 3) (%)	Risk factors
Hypersensitivity	7-22	4-10	Second dose and future doses, HLA-DRB1*07:01 polymorphism, no concurrent rituximab administration, younger age, no pre-medications
Hyperbilirubinemia	86	24-39	During the induction cycle, older age, obesity, higher dose of pegasparaginase, low albumin, low platelet count, CC genotype of rs4880 polymorphism
Pancreatitis	24	5-13	Older age, high-risk ALL stratification, germline polymorphisms in *ULK2* variant rs281366 and *RGS6* variant rs17179470
Hypertriglyceridemia	77	11-51	Beyond first cycle, high BMI, younger age
Thrombosis		11-27	First cycle, older age, obesity, mediastinal mass, cryoprecipitate replacement
Hypofibrinogenemia (<100)		48-51	First cycle, severe obesity (BMI >35)
Hyperglycemia	91	31-33	Concomitant use of steroid

BMI, body mass index.

a minimum of 2 weeks of asparagine depletion.[30] The NOPHO ALL2008 study in children used 1000 IU/m^2 pegasparaginase and reported excellent long-term outcomes with favorable toxicity.[24] The UKALL14 adult trial included 2 doses of 1000 IU/m^2 pegasparaginase during induction and observed excessive induction mortality. An amendment that omitted the first dose resulted in significantly fewer deaths at induction.[29] Nonetheless, limited data preclude a definitive answer on whether lowering the dose of pegasparaginase mitigates toxicities besides hepatotoxicity.[26] In our practice, a dose of 1000 IU/m^2 pegasparaginase is given to morbidly obese patients who have a high risk for serious liver toxicity. Other practitioners cap the dose at 3750 IU (equivalent to one vial) as a potential safety measure in patients with large body surface area to prevent excessive toxicity. Pegasparaginase is given concomitantly with other antileukemia drugs, including tyrosine kinase inhibitors as indicated. As a general rule, we recommend being faithful to the specific regimen adopted without modifications.

Recent publications on the favorable outcome of pediatric regimens (for example, the US CALGB 10403 trial[12]) will likely lead to more adult patients receiving multiple doses of pegasparaginase. However, oncologists who treat adults may still be reluctant to use pegasparaginase or may unnecessarily discontinue its administration because of adverse effects. As a result, clinical benefit of multiple pegasparaginase doses will be missed.

In 2011, an expert panel made recommendations for preventing and managing asparaginase- and pegasparaginase-associated toxicities in adults and older adolescents.[31] Because we and others have increasing experience with pegasparaginase in adults, revisiting how we approach this clinical problem is timely. The following cases illustrate how several adverse effects associated with pegasparaginase have been managed and guide whether and how to continue the drug.

Case 1: pegasparaginase-induced allergic reaction

Patient 1 is a 26-year-old female diagnosed with B-cell ALL with 46,X,t(X;14)(p22;q32), immunoglobulin H translocation, and *NRAS* mutation who was treated by using the CALGB 10403 regimen[12] and achieved a CR with persistent minimal residual disease (MRD) after induction. During consolidation, and after the third dose of intravenous pegasparaginase, she developed hypotension, swollen eyelids, chest pain, and urticarial rash. Infusion was stopped, and she received hydrocortisone, diphenhydramine, and intravenous fluids; her symptoms then resolved. She achieved MRD-negative CR.

Asparaginase is a bacterial-derived enzyme and thus can elicit an immune response manifesting as an allergic reaction, including anaphylaxis. The rate of allergic reactions in adults receiving pegasparaginase is 7% to 22%[14,18,25,32] (4% to 10% of patients have grade ≥3 reactions).[12,14,32] Pegasparaginase-induced allergic reactions usually occur early during the treatment course, typically with the second or third dose.[12,32] After an allergic reaction, asparaginase is also inactivated likely from asparaginase-induced antibodies, which may result in re-treatment failure.[33] Fortunately, after an allergic reaction to *E coli*–derived pegasparaginase, activity can be maintained by switching to *Erwinia*-derived asparaginase that has only limited cross-reactivity with *E coli*–derived asparaginase.[34]

Pegasparaginase-induced allergic reaction seems to be less common in adults than in children, but this may be a result of the use of prophylactic hydrocortisone and antihistamine pre-asparaginase in adults. Amending the adult CALGB 10403 protocol to incorporate premedication lowered the high-grade hypersensitivity reaction rate from 10% to 4%.[12] In a retrospective pediatric study, premedication resulted in reduced asparaginase-induced hypersensitivity, without excessive rates of asparaginase inactivation or substitution to *Erwinia*-derived

asparaginase.[35] Therefore, in many institutions and in ongoing trials, it has become a standard practice to administer pre-medication to adults before each pegasparaginase dose. In a genome-wide study, patients carrying HLA-DRB1*07:01 alleles had higher incidence of allergic reactions and anti-asparaginase antibodies.[36] Interestingly, there were fewer asparaginase-related allergic reactions and less switching to Erwinia-derived asparaginase in adults who were randomly assigned to rituximab in the GRAALL-2005/R study,[37] perhaps because of rituximab-induced B-cell depletion and reduction of allo-immunization toward asparaginase. In children, the rate of high-grade allergic reaction was lower after intravenous pegasparaginase than after using the intramuscular route, with potentially less antibody formation.[38]

Neutralizing antibodies and asparaginase inactivation may occur without clinical manifestations of hypersensitivity, also called "silent inactivation," which seems to be uncommon at a rate of less than 10%.[35,39,40]

The efficacy of asparaginase depends on maintaining adequate and prolonged depletion of serum asparagine. Inadequate dosing of asparaginase correlated with poor leukemia-related outcomes,[39,41] and therapeutic drug monitoring (TDM) is mostly relevant in the context of hypersensitivity.[40,42] Asparaginase activity can be measured using commercially available reagents. However, determining the minimal activity level that correlates with complete serum asparagine depletion is debatable, with reports ranging between 0.02 and 0.2 IU/mL serum asparagine.[27,39,42,43] A detailed discussion on the relationship between drug activity level and asparagine depletion is found in the recent consensus recommendations.[42] After administering pegasparaginase, the goal is to maintain therapeutic levels of asparaginase activity for 14 days or longer. Anti-asparaginase antibodies cannot be measured using commercially available reagents, and this is not a reliable technique for predicting drug inactivation because of low specificity.[40] The importance of monitoring asparaginase activity levels without clinical hypersensitivity emerges from the potential to switch to Erwinia-derived asparaginase. One pediatric study showed that detecting silent hypersensitivity by monitoring enzymatic activity of asparaginase and switching to Erwinia-derived asparaginase improved overall survival compared with those who had silent inactivation but were not switched.[39] Erwinia-derived asparaginase is recommended in favor of pegasparaginase for patients with clinical or silent hypersensitivity to maximize the clinical efficacy for pediatric regimens. Therefore, we suggest measuring enzymatic activity between days 3 and 7 after each dose. Several recently published algorithms have added specific details on measuring asparaginase activity.[44,45]

It is occasionally difficult to distinguish clinically between a mild allergic reaction to asparaginase and an infusion reaction resulting from a non-antibody–mediated process because of the rapid rise in ammonia levels post-asparaginase or preexisting anti-PEG antibodies, [33,46] which may occur after the first dose. Infusion reactions may not affect drug clearance and activity, and switching to Erwinia-derived asparaginase can be avoided. The diagnosis of allergy would be confirmed if the TDM around day 7 showed inadequate asparaginase activity.

Although premedication reduces the risk of clinical hypersensitivity, it might mask silent inactivation.[35] Although TDM is not universal, we recently implemented an approach to TDM when administering pegasparaginase intravenously with routine pre-medication to possibly avoid unmasking silent inactivation. We switched to Erwinia-derived asparaginase for clear clinical hypersensitivity such as anaphylaxis or urticaria. For mild reactions, when it is difficult to clinically distinguish between allergy and an infusion reaction, we rely on TDM to decide whether to switch to Erwinia-derived asparaginase. We use an asparaginase activity of 0.1 IU/mL as a level associated with complete asparagine depletion,[47] supported by key studies that used this level as a cutoff to switch to Erwinia-derived asparaginase.[39,48] Each dose of pegasparaginase that is not given plus the dose that caused hypersensitivity or silent inactivation is substituted by 6 doses of Erwinia-derived asparaginase over 2 weeks.[48] Recently, Erwinia-derived asparaginase has intermittently been in short supply and switching to provide the entire planned course of asparaginase may not be possible. Clinicians have taken several approaches, often on a case-by-case basis, but without data to support any strategy. Before switching, it is critical to ensure by TDM that the reaction is bona fide hypersensitivity and not an infusion reaction.

Patient 1's diagnosis of an allergic reaction was confirmed by asparaginase activity of <0.1 IU/mL on day 7 post-dosing, and all subsequent doses of pegasparaginase were replaced with Erwinia asparaginase. She tolerated Erwinia asparaginase well with no allergic reaction.

Case 2: pegasparaginase-induced hepatotoxicity

Patient 2 is a 36-year-old Hispanic female with a body mass index of 30 who was diagnosed with B-cell ALL with JAK2 mutation. She was induced according to a pediatric-inspired regimen[14] and received 2000 IU/m² pegasparaginase on day 15. Total bilirubin started to increase 1 week post-pegasparaginase and peaked 2 weeks later at 22 mg/dL (grade 4 toxicity). After 2 weeks, the bilirubin gradually declined spontaneously to grade 1. She achieved CR with persistent MRD.

Hepatotoxicity is the most common adverse effect of pegasparaginase in adults, manifesting as hyperbilirubinemia and/or transaminitis. Although uncommon in children,[49] high-grade hyperbilirubinemia (grades 3 to 4) has been reported in 24% to 39% of adults treated with pediatric regimens.[12,14,18,26,29,32] The rate of transaminitis is even higher in adults at rates of 93% for any grade and ~50% for high grade.[12,32]

The etiology of pegasparaginase-induced hepatotoxicity remains unknown, but it has several typical characteristics.[50] The toxicity is reversible, almost always unassociated with clinical liver disease, and rarely leads to liver failure. Pegasparaginase-induced hyperbilirubinemia is mostly seen during induction, with the incidence usually declining or not recurring in subsequent cycles.[12,32,50] The median duration from the time of administration of pegasparaginase until onset of high-grade hyperbilirubinemia is approximately 2 weeks, whereas the median time until toxicity recovery to grade 1 is often long and in some cases >4 weeks from the dose.[26,50] Among patients who experienced high-grade hyperbilirubinemia and were re-challenged with pegasparaginase, only 18% of all subsequent doses resulted

in the development of high-grade hyperbilirubenemia.[50,51] In a recent small study, high-grade hyperbilirubinemia occurred only after the first dose and almost never recurred.[52]

The long duration of pegasparaginase-induced high-grade hyperbilirubinemia can delay subsequent cycles, but whether this has a negative impact on outcome in adults has not yet been well studied.[26] Increased liver enzymes have less detrimental impact on treatment schedule because mild-to-moderate transaminitis does not dictate holding therapy or delaying cycles.

Risk of pegasparaginase-induced high-grade hyperbilirubinemia is linked to older age, obesity, low albumin, low platelet count, and administration of high doses of pegasparaginase.[26,29,32,51,53,54] A specific polymorphism in the *SOD2* gene (CC genotype of rs4880), a key mitochondrial enzyme that protects cells against reactive oxygen species, was associated with increased hepatotoxicity after asparaginase therapy in 1 study.[55] Hepatic steatosis is often documented in patients treated with pegasparaginase, even pretreatment,[51,53,56,57] but with little evidence of liver failure. Therefore, our routine practice is not to reduce the pegasparaginase dose for liver steatosis and not to perform routine pretreatment liver ultrasound.

Because hepatotoxicity is more frequent in adults and often manifests as a dramatic increase in bilirubin and liver enzymes, oncologists who treat adults may refrain from administering subsequent pegasparaginase doses. Because pegasparaginase is a key component of contemporary ALL regimens, this practice should be avoided because it may compromise the regimen efficacy, especially considering that hepatotoxicity is usually encountered early during induction therapy. The fact that hepatotoxicity is almost always reversible and often does not recur on subsequent doses is reassuring, and we recommend continuing pegasparaginase in subsequent cycles. The rate of high-grade hepatotoxicity is low with *Erwinia*-derived asparaginase,[34,58] but no data support switching to *Erwinia*-derived asparaginase for hepatotoxicity, and we do not recommend this practice.

Single-case observations and small case series reported that treatment with L-carnitine can result in rapid amelioration of asparaginase-induced hyperbilirubinemia.[59-62] Although this approach was successful in an animal model with pegasparaginase-induced hepatotoxicity,[63] larger studies are needed to confirm and better define this effect before L-carnitine treatment can be routinely recommended.

For pegasparaginase induced high-grade hyperbilirubinemia (grades 3 to 4), we hold drugs with known hepatotoxicity (eg, azoles or echinocandins) and adjust the dose and schedule of concurrent medications or chemotherapies that are metabolized by the liver. We also delay the next chemotherapy cycle until hyperbilirubinemia resolves to grade 1 and transaminitis is grade 2 or lower. We do not hold or reduce the pegasparaginase dose or switch to a different formulation for subsequent doses of asparaginase after high-grade hepatotoxicity. We may give L-carnitine for hyperbilirubinemia hoping to accelerate the normalization of hyperbilirubinemia and avoid excessive delay in subsequent cycles, but we acknowledge that no robust data currently support this approach. Hyperbilirubinemia at time of diagnosis is often related to liver involvement by ALL. Therefore,

we may cytoreduce with steroids and administer pegasparaginase after the bilirubin is close to normal.

Patient 2's consolidation treatment was delayed for 2 weeks because of high-grade hyperbilirubinemia. Subsequently, she started consolidation and received the second and third doses of pegasparaginase. Her bilirubin remained normal without delaying the treatment schedule. She achieved MRD-negative CR after consolidation.

Case 3: pegasparaginase-induced thrombosis

Patient 3 is a 41-year-old female diagnosed with T-cell ALL with large mediastinal mass who was induced according to a pediatric-inspired regimen,[14] and achieved CR with MRD negativity. At the end of induction, she developed swelling of the right arm; Doppler ultrasound confirmed deep vein thrombosis (DVT). She started a therapeutic dose of enoxaparin plus platelet transfusion during periods of thrombocytopenia. We replaced anti-thrombin III (ATIII) when activity level was <50% while she was receiving anticoagulation therapy.

Asparaginase predisposes patients to thrombosis because it can reduce levels of natural anticoagulants such as protein C, protein S, plasminogen, and ATIII.[64-66] In a small study, all patients developed low ATIII levels corresponding to duration of pegasparaginase activity.[27] The rate of thrombosis requiring anticoagulation in adults treated with pegasparaginase is 5% to 27%,[12,14,18,23,26,32,67] but the rate of thrombosis was reported as high as 34% in adults treated with L-asparaginase.[68] Thrombosis is predominantly venous rather than arterial.[32] It occurs more frequently during the induction cycle,[32] possibly from a higher hypercoagulable state related to active leukemia, prolonged hospitalization, and the excessive use of steroids in this cycle.[69] The risk of asparaginase-induced venous thromboembolism (VTE) increases with age, obesity, a mediastinal mass at diagnosis, and lower white blood cell counts at diagnosis.[32,67,68] Cavernous sinus thrombosis (CST) is a noteworthy rare but serious complication reported in 1% to 3% of adults treated with asparaginase and is often accompanied by superimposed intracranial bleeding (35%).[32,70] Although CST is fatal in only ~5% of patients who develop it, the event can carry significant morbidity.[70]

Treatment of pegasparaginase-induced VTE (DVT and pulmonary embolism) is the same as that for general VTE management: low molecular weight heparin started promptly and continued throughout pegasparaginase treatment and for at least 3 months. Platelet transfusion may be required early in VTE to allow the delivery of therapeutic doses of anticoagulation. One study reported that re-challenging asparaginase with anticoagulation was safe and allowed most patients to receive the intended doses of asparaginase; the overall survival was similar between patients with and without VTE.[68] In our experience, none of 10 patients who developed VTE and subsequently resumed pegasparaginase while receiving anticoagulation therapy had recurrent VTE.[32] Heparins require adequate ATIII to function. Checking and replacing ATIII while asparaginase is active during concurrent anticoagulation is physiologically conceivable and could be applied, although it is not well supported by

clinical data. We treat CST with anticoagulation therapy similar to the way we treat other acute VTEs. Anticoagulation is recommended even in cases with concomitant intracranial bleed. No strong data support the continuation of pegasparaginase after CST, and the decision may depend on the clinical severity of thrombosis in each individual patient. Because long-term neurologic consequences may occur, we recommend discontinuing pegasparaginase after CST.

Prophylactic ATIII replacement is controversial because the effect of ATIII on VTE is inconsistent in different trials. For example, ATIII replacement in the PARKAA randomized study was safe with a trend toward reducing VTE in children during L-asparaginase therapy (28% vs 37%).[71] In a retrospective analysis of adults treated with pegasparaginase, ATIII replacement did not reduce VTE rate (17% vs 11%; $P = .52$), but it did increase the overall treatment cost.[72] In contrast, the CAPELAL retrospective analysis in adults treated with L-asparaginase showed benefit with ATIII replacement on reduction of VTE risk (4.8% vs 12.2%; $P = .04$).[73] Given these results, the small number of patients in each study, inconsistency of threshold ATIII levels for replacement, different doses of ATIII given, and the high cost of ATIII replacement, our own approach is to not supplement ATIII to prevent pegasparaginase-induced thrombosis. Larger prospective studies are needed to confirm a benefit to justify the cost of ATIII replacement for VTE prevention.

Despite the high rate of pegasparaginase-induced laboratory hypofibrinogenemia (<100 mg/dL in 48% of patients), the risk of major bleeding is low overall. In fact, we and others have observed a correlation between cryoprecipitate replacement for severe hypofibrinogenemia and onset of VTE during pegasparaginase therapy.[32,74] In our experience, 35% of patients who developed VTE during pegasparaginase therapy had received cryoprecipitate replacement in the same cycle for hypofibrinogenemia.[32] Given the higher risk of thrombosis, we advise caution in routinely correcting laboratory abnormalities in the absence of active bleeding.

Another question is whether to use prophylactic anticoagulation. A recent Dana-Farber Cancer Institute ALL pediatric protocol in adults used prophylactic anticoagulation and reported lower-risk VTE (41% vs 28%; $P = .32$) without increasing high-grade bleeding (0% vs 6%; $P = .26$).[23] In a recent pediatric study, all patients received prophylaxis during induction, but those who received enoxaparin or activity-adapted ATIII replacement had a lower rate of VTE compared with those who received low-dose unfractionated heparin.[75] However, this is still controversial, and we and others so far have not taken this approach. Nonetheless, we offer enoxaparin prophylaxis to hospitalized ALL patients with an adequate platelet count.

Treatment of patient 3 resumed with all scheduled doses of pegasparaginase while she continued to receive enoxaparin. No additional DVTs were diagnosed.

Case 4: pegasparaginase-induced hypertriglyceridemia

Patient 4 is a 44-year-old female diagnosed with B-cell ALL, normal karyotype with *MLL2* mutation. She was induced with a pediatric-inspired regimen,[14] achieved MRD-negative CR, and received consolidation. A routine blood check showed hypertriglyceridemia (triglyceride level peak of 3600 mg/dL; grade 4 toxicity).

Hypertriglyceridemia is a common laboratory abnormality during asparaginase therapy. Despite high triglyceride levels (in up to ~50%),[32] in our experience, it resolves spontaneously and quickly. Pegasparaginase-induced high-grade hypertriglyceridemia usually occurs after the first cycle of induction and is more frequent during consolidation cycles.[12,32] In adults, we observed a direct correlation between risk of pegasparaginase-induced high-grade hypertriglyceridemia and increased body mass index, but we noted an inverse association with increased age.[32]

Because hypertriglyceridemia is a risk factor for pancreatitis and because both toxicities can occur post-asparaginase, clinicians may wish to treat hypertriglyceridemia to avoid pancreatitis. However, we and others have found no direct relationship between pegasparaginase-induced hypertriglyceridemia (grade or timing) and clinical pancreatitis.[32,76,77]

In our experience, hypertriglyceridemia does not require any medical intervention, and the occurrence of any grade should not delay or preclude administering subsequent doses of pegasparaginase. We offer gemfibrozil for high-grade hypertriglyceridemia, but any benefit of lowering triglyceride levels faster than the natural drop has not been established.

Pegasparaginase toxicities also include hyperglycemia, which often temporarily requires insulin. Ammonia is a product of asparaginase hydrolyzation of asparagine and hyperammonemia may manifest as transitory metabolic encephalopathy.[78-80]

Patient 4 was asymptomatic with normal serum lipase and amylase levels, and her triglyceride levels normalized within 3 weeks without intervention. Her subsequent pegasparaginase doses were also associated with asymptomatic hypertriglyceridemia that resolved without intervention. She did not experience clinical pancreatitis during therapy.

Case 5: pegasparaginase-induced pancreatitis

Patient 5 is a 22-year-old Hispanic male diagnosed with B-cell ALL with normal karyotype who was induced according to the pediatric CALGB 10403 regimen[12] and achieved MRD-negative CR. While he was receiving consolidation therapy after the second pegasparaginase dose, he developed clinical pancreatitis. Imaging showed acute interstitial edematous pancreatitis and peripancreatic fluid collection without signs of necrosis or pseudocyst. He received supportive care and his symptoms resolved.

Clinical pancreatitis occurs in 5% to 14% of adults treated with pegasparaginase[12,14,18,32]; however, chemical increase in pancreatic enzymes in the absence of symptoms or imaging findings occurs more frequently (24%).[32] Asparaginase-associated pancreatitis (AAP) can pose significant morbidities. Detailed analysis of AAP in adults is lacking. However, in

Table 2. Management and prevention of pegasparaginase toxicities

Toxicity	Management	Prevention
Hypersensitivity	Administer corticosteroid and antihistamine Replace future doses of L-asparaginase with *Erwinia* asparaginase	Pre-medicate with hydrocortisone and antihistamine Infuse slowly over 2 h
Hyperbilirubinemia	Adjust other medications and delay subsequent cycle until grade 1 is achieved Consider L-carnitine and ursodiol	Avoid hepatotoxic medications or adjust doses Not an indication to discontinue pegasparaginase or reduce the dose
Transaminitis	Consider delaying therapy for grades 3 and 4 until resolved to grade 2 Consider L-carnitine	Avoid hepatotoxic medications or adjust doses Not an indication to discontinue pegasparaginase or reduce dose
Pancreatitis	Early diagnosis and treatment Supportive medical care Further avoid asparaginase therapy of any form No intervention for chemical pancreatitis in the absence of clinical or imaging features	Avoid administering pegasparaginase or any other formulation of asparaginase after clinical asparaginase-associated pancreatitis
Hypertriglyceridemia	Consider gemfibrozil	Not an indication to discontinue pegasparaginase
Thrombosis	Anticoagulation "not clear" Maintain adequate platelet counts while patient is receiving anticoagulation	ATIII replacement for low activity level is not yet standard Prophylactic anticoagulation is controversial Not an indication to discontinue pegasparaginase Avoid replacement with cryoprecipitate to correct laboratory abnormalities in the absence of clinical bleed
Hypofibrinogenemia	Cryoprecipitate replacement only during active bleeding or before procedures	Not an indication to discontinue pegasparaginase
Hyperglycemia	Insulin and other anti-glycemic medications	Not an indication to discontinue pegasparaginase

pediatric registries for AAP, severe pancreatitis necessitating a mechanical ventilator was seen in 8%, whereas 26% to 30% of AAP patients developed pseudocyst, 25% developed necrosis, and 2% of patients died as a result.[81,82] During the acute phase of AAP, 21% of children required acute insulin therapy and 11% continued to receive insulin 1 year after the incident.[82]

The pathophysiology and predicted clinical factors for AAP remain unknown. In a systematic review, older age, pegasparaginase formulation, and high-risk ALL stratification were associated with increased risk of AAP.[83] Wolthers et al[84] observed a correlation between germline polymorphisms (*ULK2* variant rs281366, *RGS6* variant rs17179470) and increased risk of AAP, especially in children younger than age 10 years. Such genomic studies are lacking in adults.

Development of AAP is a clear contraindication for continuing pegasparaginase because the recurrence rate with re-challenging doses is 46% to 63%, with half the cases being severe.[82,85] Similarly, AAP is observed with *Erwinia*-derived asparaginase,[34] and switching the asparaginase formulation should be avoided for patients who develop AAP with the pegylated formulation. However, when lipase or amylase are increased without clinical manifestations (ie, chemical pancreatitis), asparaginase can be continued regardless of levels.

Octreotide prophylaxis was proposed to prevent AAP, but data showing efficacy of prophylaxis are limited.[86] If AAP occurs, patients benefit from early diagnosis and aggressive supportive measures, including hydration, pain control, parenteral feeding, and antimicrobial coverage. In severe cases, patients may require surgical intervention.

Pegasparaginase toxicity leading to early and permanent discontinuation (ie, because of the development of pancreatitis) can be challenging. Using a chemotherapy regimen without all prescribed asparaginase doses to treat a patient who can no longer tolerate pegasparaginase is associated with inferior outcome.[87] Current data do not provide guidance for this scenario, and we recommend addressing this problem on a case-by-case basis. For example, we might recommend consolidation with allogeneic hematopoietic cell transplantation to overcome the anticipated increased risk of relapse from omitting the remaining doses of pegasparaginase. Other clinicians might resume the chemotherapy regimen without modification aside from omitting pegasparaginase or might consider intensifying consolidation with high-dose methotrexate (ie, in protocols that use the Capizzi approach). However, this remains an important issue that will require additional studies to address.

Treatment of patient 5 was subsequently resumed, but we permanently discontinued pegasparaginase. Eventually, he started maintenance therapy, but he experienced isolated central nervous

system relapse 6 months later. He achieved remission with combination chemotherapy with frequent intrathecal chemotherapy.

In conclusion, pegasparaginase contributes to higher cure rates in adults with ALL. Although pegasparaginase is associated with unique toxicities, the majority are nonfatal, manageable, and reversible (Table 2). Careful patient education and follow-up is essential for early detection and management of the toxicities, in most cases without dose modification. Unnecessary early discontinuation or dose reduction of pegasparaginase should be avoided and may significantly compromise efficacy, which will diminish the chances of curing the patient.

Authorship

Contribution: I.A. and D.D. designed the research, analyzed the data, wrote the manuscript, and approved the final version.

Conflict-of-interest disclosure: D.D. serves on the speakers' bureau for Servier Pharmaceuticals. I.A. served on the speakers' bureau with Jazz Pharmaceuticals.

Correspondence: Dan Douer, Division of Hematology, University of Southern California, 1441 Eastlake Ave, Los Angeles, CA 90033; e-mail: douer_d@med.usc.edu.

REFERENCES

1. Larson RA, Dodge RK, Linker CA, et al. A randomized controlled trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB study 9111. Blood. 1998;92(5):1556-1564.

2. Dinmohamed AG, Szabo A, van der Mark M, et al. Improved survival in adult patients with acute lymphoblastic leukemia in the Netherlands: a population-based study on treatment, trial participation and survival. Leukemia. 2016;30(2):310-317.

3. McNeer JL, Bleyer A. Acute lymphoblastic leukemia and lymphoblastic lymphoma in adolescents and young adults. Pediatr Blood Cancer. 2018;65(6):e26989.

4. Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. J Clin Oncol. 2012;30(14):1663-1669.

5. Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood. 2008;111(4):1827-1833.

6. Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer. 2004;101(12):2788-2801.

7. Moorman AV. The clinical relevance of chromosomal and genomic abnormalities in B-cell precursor acute lymphoblastic leukaemia. Blood Rev. 2012;26(3):123-135.

8. Boissel N, Auclerc MF, Lheritier V, et al. Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. J Clin Oncol. 2003;21(5):774-780.

9. de Bont JM, Holt B, Dekker AW, van der Does-van den Berg A, Sonneveld P, Pieters R. Significant difference in outcome for adolescents with acute lymphoblastic leukemia treated on pediatric vs adult protocols in the Netherlands. Leukemia. 2004;18(12):2032-2035.

10. Ramanujachar R, Richards S, Hann I, et al. Adolescents with acute lymphoblastic leukaemia: outcome on UK national paediatric (ALL97) and adult (UKALLXII/E2993) trials. Pediatr Blood Cancer. 2007;48(3):254-261.

11. 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(5):1646-1654.

12. Stock W, Luger SM, Advani AS, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. Blood. 2019;133(14):1548-1559.

13. 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(3):526-534.

14. Douer D, Aldoss I, Lunning MA, 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(9):905-911.

15. Ribera JM, Oriol A, Sanz MA, et al. Comparison of the results of the treatment of adolescents and young adults with standard-risk acute lymphoblastic leukemia with the Programa Espanol de Tratamiento en Hematologia pediatric-based protocol ALL-96. J Clin Oncol. 2008;26(11):1843-1849.

16. Huguet F, Leguay T, Raffoux E, et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. J Clin Oncol. 2009;27(6):911-918.

17. Rijneveld AW, van der Holt B, Daenen SM, et al. Intensified chemotherapy inspired by a pediatric regimen combined with allogeneic transplantation in adult patients with acute lymphoblastic leukemia up to the age of 40. Leukemia. 2011;25(11):1697-1703.

18. Rytting ME, Thomas DA, O'Brien SM, et al. Augmented Berlin-Frankfurt-Munster therapy in adolescents and young adults (AYAs) with acute lymphoblastic leukemia (ALL). Cancer. 2014;120(23):3660-3668.

19. Sallan SE, Hitchcock-Bryan S, Gelber R, Cassady JR, Frei E III, Nathan DG. Influence of intensive asparaginase in the treatment of childhood non-T-cell acute lymphoblastic leukemia. Cancer Res. 1983;43(11):5601-5607.

20. Nachman JB, Sather HN, Sensel MG, et al. Augmented post-induction therapy for children with high-risk acute lymphoblastic leukemia and a slow response to initial therapy. N Engl J Med. 1998;338(23):1663-1671.

21. Amylon MD, Shuster J, Pullen J, et al. Intensive high-dose asparaginase consolidation improves survival for pediatric patients with T cell acute lymphoblastic leukemia and advanced stage lymphoblastic lymphoma: a Pediatric Oncology Group study. Leukemia. 1999;13(3):335-342.

22. Douer D. Is asparaginase a critical component in the treatment of acute lymphoblastic leukemia? Best Pract Res Clin Haematol. 2008;21(4):647-658.

23. Grace RF, DeAngelo DJ, Stevenson KE, et al. The use of prophylactic anticoagulation during induction and consolidation chemotherapy in adults with acute lymphoblastic leukemia. J Thromb Thrombolysis. 2018;45(2):306-314.

24. Albertsen BK, Grell K, Abrahamsson J, et al. Intermittent versus continuous PEG-asparaginase to reduce asparaginase-associated toxicities: A NOPHO ALL2008 randomized study. J Clin Oncol. 2019;37(19):1638-1646.

25. DeAngelo DJ, Stevenson K, Neuberg DS, et al. A multicenter phase II study using a dose intensified pegylated-asparaginase pediatric regimen in adults with untreated acute lymphoblastic leukemia: A DFCI ALL Consortium

trial [abstract]. *Blood.* 2015;126(23). Abstract 80.

26. Goekbuget N, Baumann A, Beck J, et al. PEG-asparaginase intensification in adult acute lymphoblastic leukemia (ALL): Significant improvement of outcome with moderate increase of liver toxicity in the German Multicenter Study Group for Adult ALL (GMALL) study 07/2003 [abstract]. *Blood.* 2010;116(21). Abstract 494.

27. Douer D, Yampolsky H, Cohen LJ, et al. Pharmacodynamics and safety of intravenous pegaspargase during remission induction in adults aged 55 years or younger with newly diagnosed acute lymphoblastic leukemia. *Blood.* 2007;109(7):2744-2750.

28. Gökbuget N, Kneba M, Raff T, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. *Blood.* 2012;120(9):1868-1876.

29. Patel B, Kirkwood AA, Dey A, et al. Pegylated-asparaginase during induction therapy for adult acute lymphoblastic leukaemia: toxicity data from the UKALL14 trial. *Leukemia.* 2017; 31(1):58-64.

30. Appel IM, Kazemier KM, Boos J, et al. Pharmacokinetic, pharmacodynamic and intracellular effects of PEG-asparaginase in newly diagnosed childhood acute lymphoblastic leukemia: results from a single agent window study. *Leukemia.* 2008;22(9): 1665-1679.

31. 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(12):2237-2253.

32. 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(4): 375-380.

33. Liu Y, Smith CA, Panetta JC, et al. Antibodies predict pegaspargase allergic reactions and failure of rechallenge. *J Clin Oncol.* 2019; 37(23):2051-2061.

34. Plourde PV, Jeha S, Hijiya N, et al. Safety profile of asparaginase Erwinia chrysanthemi in a large compassionate-use trial. *Pediatr Blood Cancer.* 2014;61(7):1232-1238.

35. Cooper SL, Young DJ, Bowen CJ, Arwood NM, Poggi SG, Brown PA. Universal premedication and therapeutic drug monitoring for asparaginase-based therapy prevents infusion-associated acute adverse events and drug substitutions. *Pediatr Blood Cancer.* 2019;66(8):e27797.

36. Fernandez CA, Smith C, Yang W, et al. HLA-DRB1*07:01 is associated with a higher risk of asparaginase allergies. *Blood.* 2014;124(8): 1266-1276.

37. Maury S, Chevret S, Thomas X, et al. Rituximab in B-lineage adult acute lymphoblastic leukemia. *N Engl J Med.* 2016;375(11): 1044-1053.

38. Burke MJ, Devidas M, Maloney K, et al. Severe pegaspargase hypersensitivity reaction rates (grade >/=3) with intravenous infusion vs. intramuscular injection: analysis of 54,280 doses administered to 16,534 patients on children's oncology group (COG) clinical trials. *Leuk Lymphoma.* 2018;59(7):1624-1633.

39. Vrooman LM, Stevenson KE, Supko JG, et al. Postinduction dexamethasone and individualized dosing of Escherichia coli L-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: results from a randomized study–Dana-Farber Cancer Institute ALL Consortium Protocol 00-01. *J Clin Oncol.* 2013;31(9):1202-1210.

40. Tong WH, Pieters R, Kaspers GJ, et al. A prospective study on drug monitoring of PEGasparaginase and Erwinia asparaginase and asparaginase antibodies in pediatric acute lymphoblastic leukemia. *Blood.* 2014; 123(13):2026-2033.

41. Pession A, Valsecchi MG, Masera G, et al. Long-term results of a randomized trial on extended use of high dose L-asparaginase for standard risk childhood acute lymphoblastic leukemia. *J Clin Oncol.* 2005;23(28): 7161-7167.

42. van der Sluis IM, Vrooman LM, Pieters R, et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. *Haematologica.* 2016;101(3): 279-285.

43. Schore RJ, Devidas M, Bleyer A, et al. Plasma asparaginase activity and asparagine depletion in acute lymphoblastic leukemia patients treated with pegaspargase on Children's Oncology Group AALL07P4. *Leuk Lymphoma.* 2019;60(7):1740-1748.

44. Salzer W, Bostrom B, Messinger Y, Perissinotti AJ, Marini B. Asparaginase activity levels and monitoring in patients with acute lymphoblastic leukemia. *Leuk Lymphoma.* 2018;59(8): 1797-1806.

45. Marini BL, Perissinotti AJ, Bixby DL, Brown J, Burke PW. Catalyzing improvements in ALL therapy with asparaginase. *Blood Rev.* 2017; 31(5):328-338.

46. Burke MJ, Rheingold SR. Differentiating hypersensitivity versus infusion-related reactions in pediatric patients receiving intravenous asparaginase therapy for acute lymphoblastic leukemia. *Leuk Lymphoma.* 2017;58(3): 540-551.

47. 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(6): 1986-1994.

48. Salzer WL, Asselin B, Supko JG, et al. Erwinia asparaginase achieves therapeutic activity after pegaspargase allergy: a report from the Children's Oncology Group. *Blood.* 2013; 122(4):507-514.

49. 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(16):1677-1690.

50. Burke PW, Aldoss I, Lunning MA, 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.

51. Rausch CR, Marini BL, Benitez LL, et al. PEGging down risk factors for peg-asparaginase hepatotoxicity in patients with acute lymphoblastic leukemia (dagger). *Leuk Lymphoma.* 2018;59(3):617-624.

52. Geyer MB, Ritchie EK, Rao AV, et al. Pediatric-inspired chemotherapy incorporating pegaspargase is safe and results in high rates of MRD negativity in adults ages 18-60 with Philadelphia chromosome-negative acute lymphoblastic leukemia and lymphoblastic lymphoma [abstract]. *Blood.* 2018;132(suppl 1). Abstract 4013.

53. Christ TN, Stock W, Knoebel RW. Incidence of asparaginase-related hepatotoxicity, pancreatitis, and thrombotic events in adults with acute lymphoblastic leukemia treated with a pediatric-inspired regimen. *J Oncol Pharm Pract.* 2018;24(4):299-308.

54. Denton CC, Rawlins YA, Oberley MJ, Bhojwani D, Orgel E. Predictors of hepatotoxicity and pancreatitis in children and adolescents with acute lymphoblastic leukemia treated according to contemporary regimens. *Pediatr Blood Cancer.* 2018;65(3):e26891.

55. 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(3): 274-279.

56. Sahoo S, Hart J. Histopathological features of L-asparaginase-induced liver disease. *Semin Liver Dis.* 2003;23(3):295-300.

57. Kamal N, Koh C, Samala N, et al. Asparaginase-induced hepatotoxicity: rapid development of cholestasis and hepatic steatosis. *Hepatol Int.* 2019;13(5):641-648.

58. Horvat TZ, Pecoraro JJ, Daley RJ, et al. The use of Erwinia asparaginase for adult patients with acute lymphoblastic leukemia after pegaspargase intolerance. *Leuk Res.* 2016;50: 17-20.

59. 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(7):1670-1674.

60. Alshiekh-Nasany R, Douer D. L-carnitine for treatment of pegasparaginase-induced hepatotoxicity. *Acta Haematol.* 2016;135(4): 208-210.

61. Özdemir ZC, Turhan AB, Eren M, Bor O. Is N-acetylcysteine infusion an effective treatment option in L-asparaginase associated hepatotoxicity? *Blood Res.* 2017;52(1):69-71.

62. Lu G, Karur V, Herrington JD, Walker MG. Successful treatment of pegaspargase-induced acute hepatotoxicity with vitamin B

complex and L-carnitine. *Proc Bayl Univ Med Cent.* 2016;29(1):46-47.

63. 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(3):167-175.

64. Payne JH, Vora AJ. Thrombosis and acute lymphoblastic leukaemia. *Br J Haematol.* 2007;138(4):430-445.

65. Truelove E, Fielding AK, Hunt BJ. The co-agulopathy and thrombotic risk associated with L-asparaginase treatment in adults with acute lymphoblastic leukaemia. *Leukemia.* 2013;27(3):553-559.

66. Leone G, Gugliotta L, Mazzucconi MG, et al. Evidence of a hypercoagulable state in patients with acute lymphoblastic leukemia treated with low dose of E. coli L-aspar-aginase: a GIMEMA study. *Thromb Haemost.* 1993;69(1):012-015.

67. Rank CU, Toft N, Tuckuviene R, et al. Thromboembolism in acute lymphoblastic leukemia: results of NOPHO ALL2008 pro-tocol treatment in patients aged 1 to 45 years. *Blood.* 2018;131(22):2475-2484.

68. Grace RF, Dahlberg SE, Neuberg D, et al. The frequency and management of asparaginase-related thrombosis in paediatric and adult patients with acute lymphoblastic leukaemia treated on Dana-Farber Cancer Institute consortium protocols. *Br J Haematol.* 2011; 152(4):452-459.

69. Nowak-Göttl U, Heinecke A, von Kries R, Nurnberger W, Munchow N, Junker R. Thrombotic events revisited in children with acute lymphoblastic leukemia: impact of concomitant Escherichia coli asparaginase/prednisone administration. *Thromb Res.* 2001; 103(3):165-172.

70. Couturier MA, Huguet F, Chevallier P, et al. Cerebral venous thrombosis in adult patients with acute lymphoblastic leukemia or lym-phoblastic lymphoma during induction che-motherapy with l-asparaginase: The GRAALL experience. *Am J Hematol.* 2015;90(11): 986-991.

71. Mitchell L, Andrew M, Hanna K, et al. Trend to efficacy and safety using antithrombin concentrate in prevention of thrombosis in children receiving l-asparaginase for acute lymphoblastic leukemia. Results of the PAARKA study. *Thromb Haemost.* 2003;90(2): 235-244.

72. Chen J, Ngo D, Aldoss I, Shayani S, Tsai NC, Pullarkat V. Antithrombin supplementation did not impact the incidence of pegylated asparaginase-induced venous thromboem-bolism in adults with acute lymphoblastic leukemia. *Leuk Lymphoma.* 2019;60(5): 1187-1192.

73. Hunault-Berger M, Chevallier P, Delain M, et al. Changes in antithrombin and fibrinogen levels during induction chemotherapy with L-asparaginase in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma. Use of supportive coagulation therapy and clinical outcome: the CAPELAL study. *Haematologica.* 2008;93(10): 1488-1494.

74. Orvain C, Balsat M, Lhéritier V, et al. Prevention of venous thrombotic events in adult patients with acute lymphoblastic leu-kemia treated in a pediatric-inspired protocol - a GRAALL Study [abstract]. *Blood.* 2016; 128(22). Abstract 2776.

75. Greiner J, Schrappe M, Claviez A, et al. THROMBOTECT - a randomized study com-paring low molecular weight heparin, anti-thrombin and unfractionated heparin for thromboprophylaxis during induction therapy of acute lymphoblastic leukemia in children and adolescents. *Haematologica.* 2019; 104(4):756-765.

76. Persson L, Harila-Saari A, Hed Myrberg I, Heyman M, Nilsson A, Ranta S. Hypertriglyceridemia during asparaginase treatment in children with acute lymphoblastic leukemia correlates with antithrombin activity in adolescents. *Pediatr Blood Cancer.* 2017; 64(10):e26559.

77. Raja RA, Schmiegelow K, Sorensen DN, Frandsen TL. Asparaginase-associated pan-creatitis is not predicted by hyper-triglyceridemia or pancreatic enzyme levels in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer.* 2017;64(1):32-38.

78. Nussbaum V, Lubcke N, Findlay R. Hyperammonemia secondary to asparaginase: A case series. *J Oncol Pharm Pract.* 2016;22(1):161-164.

79. Jörck C, Kiess W, Weigel JF, Mutze U, Bierbach U, Beblo S. Transient hyper-ammonemia due to L-asparaginase therapy in children with acute lymphoblastic leukemia or non-Hodgkin lymphoma. *Pediatr Hematol Oncol.* 2011;28(1):3-9.

80. Sudour H, Schmitt C, Contet A, Chastagner P, Feillet F. Acute metabolic encephalopathy in two patients treated with asparaginase and ondasetron. *Am J Hematol.* 2011;86(3): 323-325.

81. Raja RA, Schmiegelow K, Albertsen BK, et al. Asparaginase-associated pancreatitis in chil-dren with acute lymphoblastic leukaemia in the NOPHO ALL2008 protocol. *Br J Haematol.* 2014;165(1):126-133.

82. Wolthers BO, Frandsen TL, Baruchel A, et al. Asparaginase-associated pancreatitis in childhood acute lymphoblastic leukaemia: an observational Ponte di Legno Toxicity Work-ing Group study. *Lancet Oncol.* 2017;18(9): 1238-1248.

83. Oparaji JA, Rose F, Okafor D, et al. Risk factors for asparaginase-associated pancreatitis: A systematic review. *J Clin Gastroenterol.* 2017; 51(10):907-913.

84. Wolthers BO, Frandsen TL, Abrahamsson J, et al. Asparaginase-associated pancreatitis: a study on phenotype and genotype in the NOPHO ALL2008 protocol. *Leukemia.* 2017; 31(2):325-332.

85. Kearney SL, Dahlberg SE, Levy DE, Voss SD, Sallan SE, Silverman LB. Clinical course and outcome in children with acute lymphoblastic leukemia and asparaginase-associated pan-creatitis. *Pediatr Blood Cancer.* 2009;53(2): 162-167.

86. Sakaguchi S, Higa T, Suzuki M, Fujimura J, Shimizu T. Prophylactic use of octreotide for asparaginase-induced acute pancreatitis. *Int J Hematol.* 2017;106(2):266-268.

87. Gupta S, Wang C, Raetz EA, et al. Impact of asparaginase discontinuation on out-come in childhood ALL: A report from the Children's Oncology Group (COG). *J Clin Oncol.* 2019;37(15 suppl). Abstract 10005.