


Asparaginase in the Treatment of Acute Lymphoblastic Leukemia in Adults: Current Evidence and Place in Therapy

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Abstract: Acute lymphoblastic leukemia (ALL) is a rare hematologic malignancy resulting in the production of abnormal lymphoid precursor cells. Occurring in B-cell and T-cell subtypes, ALL is more common in children, comprising nearly 30% of pediatric malignancies, but also constitutes 1% of adult cancer diagnoses. Outcomes are age-dependent, with five-year overall survival of greater than 90% in children and less than 20% in older adults. L-asparaginase, an enzyme not found in humans, depletes serum levels of L-asparagine. As leukemic cells are unable to synthesize this amino acid, its deprivation results in cell death. The success of asparaginase-containing regimens in the treatment of pediatric ALL, and poor outcomes with conventional cytotoxic regimens in adults, have led to trials of pediatric or pediatric-inspired regimens incorporating asparaginase in the adolescent and young adult (AYA) and adult populations. Initially purified from *Escherichia coli*, newer formulations of asparaginase have been developed to address short half-life, high immunogenic potential, and manufacturing difficulties. Unfamiliarity with asparaginase use and management of its unique toxicities may result in treatment-decisions that negatively impact outcomes. In this review, we address the current use of asparaginase in the treatment of ALL, with an emphasis on its role in the treatment of adults, key clinical trials, recognition and management of toxicities, and ongoing directions of study.

Keywords: acute lymphoblastic leukemia, ALL, adult, asparaginase, pegaspargase

Introduction

Acute lymphoblastic leukemia (ALL) is a hematologic malignancy of lymphoid precursor cells occurring in B- and T-cell subtypes. While it is the most common childhood malignancy, comprising up to 30% of pediatric cancer and 80% of pediatric leukemia diagnoses, it is relatively rare among adults, comprising 15–20% of adult leukemia cases and less than 1% of adult cancer diagnoses in the United States (US).¹ Historically, significantly better outcomes have been seen in pediatric patients, with a five-year overall survival (OS) of nearly 90% in children, and less than 20% for older patients. This is thought to be due in part to the regimens used in the pediatric population, which generally include agents with more frequent and longer durations of administration, though differences in host and disease factors between the two groups are also likely contributory. Non-randomized studies also noted that adolescent and young adults (AYA) treated by pediatricians with expertise in these regimens had better outcomes than those treated by adult oncologists.²⁻⁷ These findings have led to further trials of pediatric or pediatric-inspired regimens in AYA and adult patients. L-asparaginase is a central component of most modern pediatric ALL regimens. Therefore, the migration of pediatric strategies into the management of adults with ALL will lead to the wider utilization of this class of agents in this population. Here, we review the role of asparaginase in the treatment of ALL, with an emphasis on its use in the AYA and adult population, the various formulations currently available, its unique side-effect profile, management of treatment-related toxicity, and ongoing clinical trials.

Historical Perspective

The first studies implicating L-asparaginase as an anti-leukemic agent were conducted in the 1950s and 1960s. Kidd⁸ demonstrated that guinea pig serum could induce regression of explanted lymphomas in mice and rats, with a subsequent series of studies identifying L-asparaginase as the serum component responsible for this effect.^{9–13} The first documented use of L-asparaginase in humans came in 1966. Dolowy¹⁴ reported a case of a pediatric patient with multiply relapsed ALL who was administered L-asparaginase partially purified from guinea pig serum. While improvement of clinical and laboratory parameters was noted, the patient developed significant toxicity immediately following infusion, including a likely hypersensitivity reaction, and succumbed to pulmonary hemorrhage ten days after administration. In a 1967 case series, Hill reported¹⁵ on three pediatric patients with ALL treated with purified L-asparaginase, all of whom exhibited clinical and laboratory improvement, with one achieving complete remission (CR). These preliminary reports led to larger-scale studies in children, which were able to be conducted following the availability in 1978 of commercially produced L-asparaginase from *Escherichia coli* (*E. coli*). Early studies¹⁶ in adults were also performed; however, significant toxicities led to the avoidance of its use in subsequent trials. Consequently, the role of L-asparaginase in the treatment of this population was not readdressed until several years later.

Pharmacology

Asparagine is one of twenty amino acids necessary for cell function and survival. It is generated in normal cells by L-asparagine synthetase, which catalyzes the conversion of aspartic acid and glutamine to asparagine and glutamate.¹⁷ This enzyme is poorly expressed in leukemic cells, which rely on serum asparagine to fulfill the increased demand of sustained malignant cell growth and proliferation.¹⁸ L-asparaginase is an amidase that removes serum asparagine from circulation by hydrolyzing L-asparagine into aspartic acid and ammonia.¹⁹ Without an exogenous source of asparagine, protein synthesis is quickly inhibited in the tumor cell, subsequently leading to apoptosis (Figure 1).

Asparaginase Formulations

Native *Escherichia coli* Asparaginase

While absent in humans, L-asparaginase exists in various animals, plants, and microorganisms.¹⁹ As noted above, the first commercial L-asparaginase product, FDA-approved in 1978, was isolated from several *E. coli* strains.^{19,20} Despite its efficacy in killing leukemic cells, the use of this formulation was hampered by its short half-life, necessitating frequent dosing, as well as high rate of immunogenicity.^{18,21,22}

Pegylated Asparaginase (Pegaspargase, Calaspargase Pegol)

Pegaspargase, comprised of polyethylene glycol (PEG) conjugated to L-asparaginase through a succinimidyl succinate linker, emerged in the 1990s to address the above limitations.^{21–23} This formulation has an extended plasma half-life, allowing it to be dosed every two weeks rather than thrice weekly. Moreover, the incorporation of the PEG moiety decreases its immunogenicity; however, patients can develop antibodies against the linker.²⁴ Compared to the >30% incidence rate seen with native enzyme, clinical allergic reactions with pegaspargase occurred in 3% of first-line and 10% of relapsed ALL patients without prior reactions.^{18,25,26}

Calaspargase pegol, a novel pegylated preparation, was approved for the treatment of children and young adults with ALL in 2018.²⁷ The use of a succinimidyl carbonate linker to covalently bind *E. coli* L-asparaginase and PEG, results in increased stability and longer half-life allowing for every-third-week dosing.²³

Erwinia chrysanthemi (Native and Recombinant) Asparaginase

Despite the improved convenience and toxicity profile of pegaspargase, the need for an alternative L-asparaginase remained for those who developed hypersensitivity to *E. coli*-derived L-asparaginases. *Erwinia* L-asparaginase, which does not share cross-reactivity with *Escherichia* enzyme, was approved in 2011 for this patient population.¹⁹ In the AALL07P2 trial, 93% of patients with clinical allergy to pegaspargase achieved therapeutic activity with *Erwinia* L-asparaginase.²⁸ However, as the product was manufactured on a batch-by-batch basis, its clinical impact was constrained by drug shortages.²⁹ To combat this, efforts were undertaken to develop a bioengineered version,²⁹ and in

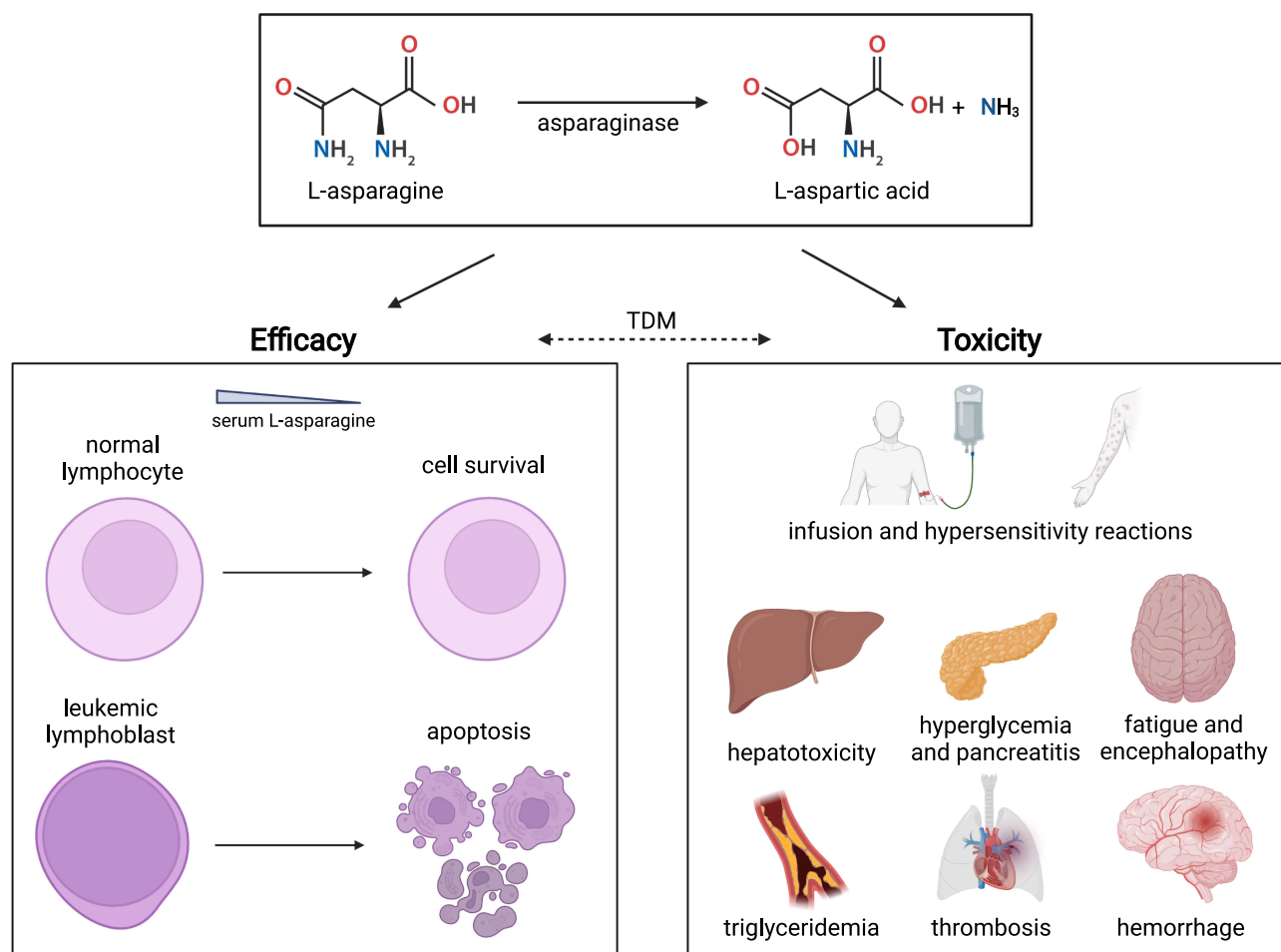


Figure 1 Depiction of the pharmacologic effects of asparaginase. Asparaginase catalyzes (top panel) the degradation of L-asparagine to L-aspartic acid and ammonia (NH₃). Unlike normal cells, which express asparagine synthetase, leukemic cells are unable to generate L-asparagine, so its serum depletion results in apoptosis (left panel). Toxicities due to asparaginase (right panel) occur through a variety of mechanisms including decreased protein synthesis, direct effects on metabolites, or more complex mechanisms. Therapeutic drug monitoring (TDM) may allow for individualized asparaginase dosing and maximization of treatment efficacy with reduction of toxicity, but this is not yet widely practiced. Created with BioRender.com.

2021, recombinant *Erwinia* L-asparaginase, manufactured using a *Pseudomonas fluorescens* expression platform, received FDA approval.^{29,30}

Pharmacokinetics

L-asparaginase mostly resides in the vascular space upon administration, as demonstrated by its small volume of distribution (Table 1), with minimal enzyme detected in pleural and peritoneal fluids.^{18,31} Enzymatic activity can also be measured in cerebrospinal fluid (CSF), where extent and duration of asparagine depletion have been associated with treatment outcomes.^{31,32}

L-asparaginase is thought to be metabolized via proteolytic enzymes in tissues.^{22,30} It is not excreted renally.³¹ The PEG moiety increases steric hindrance, limiting access of circulating peptidases and proteases,³³ and thereby significantly extending half-life. *Erwinia* formulations have shorter half-lives than their *E. coli* counterparts and therefore require more frequent administration to achieve similar therapeutic effects.^{26,34,35}

Pharmacodynamics and Therapeutic Drug Monitoring

The primary goal of L-asparaginase therapy is total asparagine depletion in the blood and CSF.^{22,26} However, it is difficult to measure serum asparagine concentration consistently and accurately due to technical and logistical constraints.²⁶ Since there is a direct correlation between the level of L-asparaginase activity and reduction in asparagine

Table 1 Pharmacokinetic Properties of L-Asparaginase Products

	<i>E. coli</i> Asparaginase (Native)	Pegaspargase	Calaspargase Pegol	<i>Erwinia</i> Asparaginase (Native)	<i>Erwinia</i> Asparaginase (Recombinant)
Common dose range	6000–25,000 IU/m ²	2000–2500 IU/m ²	2500 IU/m ²	25,000 IU/m ²	25 mg/m ²
Administration frequency	1–3x/week	Every 2 weeks	Every 3 weeks	3x/week	Every 48 hr
Bioavailability	IM: ~50% IV: 100%	IM: 82–98% IV: 100%	IV: 100%	IM: 37% IV: 100%	IM: 37%
Volume of distribution (L)	–	1.86–2	2.96	–	1.48
Half-life	IM: 34–49 hr IV: 8–30 hr	IM: 5.8 days IV: 5.3 days	IV: 16.1 days	IM: 16 hr IV: 7.5 hr	IM: 18.2 hr

Note: References: 22, 24, 25, 29, 32, 34.

concentration, serum asparaginase activity (SAA) has become a clinical surrogate to predict pharmacodynamic success.^{26,34,36} SAA ≥ 0.1 IU/mL was proposed as the minimum threshold for meaningful efficacy, following a 1981 study demonstrating that plasma and CSF asparaginase were undetectable at this level. This has been subsequently validated in multiple studies.^{26,37}

Asparaginase in Pediatric ALL

In the years following initial reports suggesting a role for L-asparaginase in ALL therapy, as detailed below and in Table 1, several clinical trials were performed to assess safety, efficacy, and optimal dosing of different forms of asparaginase when combined with chemotherapy in pediatric cohorts. These studies ultimately demonstrated improved outcomes, and the inclusion of asparaginase has now become standard of care in pediatric patients. The current paradigm of pediatric ALL management is divided into discrete phases of multiagent chemotherapy: remission induction, intensive consolidation including CNS-directed therapy, delayed-intensification, and low-intensity maintenance chemotherapy.³⁸ Asparaginase is typically incorporated into induction, consolidation, and intensification stages. While this review focuses on asparaginase in adult ALL, we discuss several key pediatric studies here (summarized in Table 2) to provide important context. For more details, we refer the interested reader to other reviews on this topic.^{39,40}

Several studies assessed the addition of asparaginase to standard chemotherapy in either induction or intensification phases. In the US Children's Cancer Study Group (CCG) 101/143 trial,⁴¹ patients received native *E. coli* L-asparaginase in addition to vincristine and prednisone during induction, with a statistically significant improvement in CR rate and decrease in treatment failure rate, compared to patients receiving only vincristine and prednisone in the prior CCG 903 trial. The prospective Dana Farber Cancer Institute (DCFI) 77–01 study⁴² half of the patients were randomized to receive weekly high-dose L-asparaginase during intensification with improvement in disease-free survival (DFS) in patients receiving L-asparaginase. The subsequent DCFI 88–01 study⁴³ also noted improved event-free survival (EFS) in patients receiving high-dose L-asparaginase during intensification/continuation cycles.

The Pediatric Oncology Group (POG) 8704 study addressed patients with T-cell ALL.⁴⁴ Patients were treated with rotating combinations of chemotherapy including L-asparaginase followed by randomization to receive or not receive weekly. Those who were randomized to receive asparaginase noted significant improvement in four-year continuous CR rate, though at the expense of increased toxicities.

The Italian, Dutch, Hungarian (IDH) ALL-91 study⁴⁵ assessed whether the addition of weekly high-dose L-asparaginase (25,000 IU/m²) to a modified Berlin-Frankfurt-Muenster (BFM) backbone and demonstrated improved ten-year DFS in those receiving L-asparaginase. Uniquely, >90% of patients received *Erwinia* asparaginase due to unavailability of *E. coli* asparaginase.

Several studies assessed whether increased L-asparaginase intensity would improve outcomes as well as the efficacy of pegaspargase versus native *E. coli* enzyme. In the POG 9310 study,⁴⁶ patients with relapsed B-ALL were randomized to receive pegaspargase (2500 IU/m²) either weekly (four doses) or biweekly (two doses), during reinduction. The overall

Table 2 Selected Pediatric Studies Incorporating Asparaginase in ALL Treatment Regimens

Study (Design)	Enrollment Period	Age Range	Number (Evaluable)	Disease (Status)	Asparaginase Formulation	Treatment Phase and Dosing	Selected Outcomes	Selected Events Including Asparaginase-Related Toxicities
CCG 101/143 (Non-randomized prospective)	1971 – NR	< 16	823 (815)	ALL or AUL (untreated)	Native <i>E. coli</i>	Induction 6000 IU/m ² IM 3/week (9 doses)	CR 93% versus 86% in CCG 903	Death during induction – 26 (3.2%) L-asparaginase discontinued due to associated toxicities – 2 (0.25%) L-asparaginase-related not requiring cessation – 35 (4.3%) Hyperglycemia – 20 (2.5%) Allergic reactions – 6 (0.74%) Hypofibrinogenemia – 4 (0.49%) Pancreatitis – 4 (0.49%) Hepatotoxicity – 1 (0.12%)
DFCI 77-01 (Randomized prospective)	1977–1979	< 20	74 (72)	Non-T-cell ALL or AUL (untreated)	Native <i>E. coli</i>	Early consolidation (all patients) Age < 6: 50,000 IU/m ² IV QOD Age ≥ 6: 25,000 IU/m ² IV QOD (5 doses) Intensification (if randomized) Age < 6: 50,000 IU/m ² IV weekly Age ≥ 6: 25,000 IU/m ² IV weekly (until cumulative doxorubicin dose reached)	DFS 72% (asp) versus 42% (no asp) p = 0.04 DFS 86% (SR) DFS 64% (HR)	Pancreatitis – 3 (4.2%) Hepatitis – 2 (2.8%) Hypersensitivity – 1 (1.4%)
DCFI 88-01 (Non-randomized prospective)	1981–1985	≤ 18	289 (289)	ALL (untreated)	Native <i>E. coli</i>	Intensification SR: 25,000 IU/m ² IM weekly (20 doses) HR: 25,000 IU/m ² IM weekly (until cumulative doxorubicin dose reached)	Overall: 4Y EFS 77% SR: 4Y EFS 86% HR: 4Y EFS 71% p = 0.003	Allergy to <i>E. coli</i> – 54 (19%) Allergy to <i>Erwinia</i> – 9 (17%) Hyperamylasemia – 16 (6%) Pancreatitis – 11 (4%) Stroke – 8 (3%) Hyperlipidemia – 3 (1%) Thrombophlebitis – 3 (1%) Hepatitis – 1 (<1%) PE – 1 (<1%) Encephalopathy – 2 (<1%)

(Continued)

Table 2 (Continued).

Study (Design)	Enrollment Period	Age Range	Number (Evaluable)	Disease (Status)	Asparaginase Formulation	Treatment Phase and Dosing	Selected Outcomes	Selected Events Including Asparaginase-Related Toxicities
POG 8704 (Randomized prospective)	1987–1992	1–21	552 (484)	Untreated T-cell ALL and advanced LBL	Native <i>E. coli</i>	Induction 10,000 U/m ² IM D27, 29, 31 Consolidation (if randomized) 25,000 IU/m ² IM weekly x 20 doses	Overall: 4Y CCR 71.3% (asp) vs 57.8% (no-asp), p < 0.001 T-ALL: 4Y CCR 68% (asp) vs 55% (no-asp), p = 0.002 LBL: 4Y CCR 78% (asp) vs 64% (no-asp), p = 0.048	Asp cohort vs no-asp cohort: Allergic reactions – 24% vs 10% Pancreatitis – 0.82% vs 0.10%, p < 0.001 Elevated transaminases – 2.6% vs 0.9%, p < 0.001 Bilirubin elevation – 1.2% vs 0.05%, p < 0.001 Thrombocytopenia – 6.2% vs 2.6%, p < 0.001
IDH-ALL-91 (Randomized prospective)	1991–1997	1–15	494 (490)	SR non-T-cell ALL (untreated)	Native <i>E. coli</i> <i>Erwinia</i>	Induction/Reinduction 10,000 U/m ² D8, 15, 22, 29 Continuation (if randomized) 25,000 U/m ² weekly (20 doses)	Asp vs no-asp cohorts: 10Y DFS 87.5% vs 78.7% p = 0.03 Hazard ratio 0.60 (90% CI 0.38–0.93) 10Y survival estimate 93.7% vs 88.6%, p = 0.05	Allergic reactions ~10% (~3% required discontinuation)
POG 9310 (Randomized prospective)	NR	< 22	148 (147)	B-cell ALL (first relapse)	Pegaspargase	Induction (randomized) 2500 U/m ² IM Weekly (4 doses) or biweekly (2 doses)	CR: 90% (overall) 97% (weekly) vs 82% (biweekly), p = 0.003	Hypofibrinogenemia – 32 (25%) hypoalbuminemia – 29 (20%) elevated bilirubin – 22 (15%) elevated ALT – 13 (9%) hypersensitivity – 6 (4%) hyperglycemia – 5 (3%) thrombotic events – 3 (2%) CNS events – 3 (2%) clinical pancreatitis – 2 (1%) (No significant difference between groups)

DFCI 91-01 (Randomized prospective)	1991-1995	0-18	386 (377)	ALL (untreated)	Native <i>E. coli</i> Pegaspargase	Intensification (randomized) 25,000 IU/m ² IM weekly <i>E. coli</i> (30 doses) 2500 IU/m ² IM biweekly pegaspargase (15 doses)	Overall 5Y EFS: 83% ± 2% 5Y EFS (weeks of asp): 90% ± 2% (≤ 25) vs 73% ± 7% (≥ 26), p < 0.01 5Y EFS (asp formulation): 84% ± 4% (<i>E. coli</i>) vs 78% ± 4% (pegaspargase), p = 0.29	Any asparaginase related toxicity – 29% allergic reactions – 15% pancreatitis – 7% coagulopathy – 4.5% CNS thrombosis – 1% Asparaginase-related toxicity by age: 48% (9-18) vs 24% (<9), p < 0.01
COG AALL0232 (Randomized prospective 2 x 2 factorial)	2004-2011	1-30	3154 (2554)	B-cell ALL (untreated)	Pegaspargase	Induction/Extended induction 2500 IU/m ² D4, 5, or 6 Consolidation 2500 IU/m ² D15, 43 Interim Maintenance (if randomized) 2500 IU/m ² D2, 22	HD-MTX vs C-MTX 5Y EFS 82% vs 75.4%, p = 0.006	NR
COG AALL0434 (Randomized prospective 2 x 2 pseudofactorial)	2007-2014	1-31	1895 (1189)	T-cell ALL (untreated)	Pegaspargase	Induction 2500 IU/m ² D4, 5, or 6 Consolidation 2500 IU/m ² D15, 43 Interim Maintenance (C-MTX, if randomized) 2500 IU/m ² D2, 22	C-MTX vs HD-MTX 5Y DFS: 91.5% (95% CI 88.1-94.8) vs 85.3% (95% CI 81.0-89.5%), p = 0.005 5Y OS 93.7% (95% CI 90.8-96.6%) vs 89.4% (95% CI 85.7-93.2%), p = 0.04	NR

Note: References: 40-48.

Abbreviations: ALL, acute lymphoblastic leukemia; ALT, alanine aminotransferase; AUL, acute undifferentiated leukemia; asp, asparaginase; CCG, Children's Cancer Study Group; COG, Children's Oncology Group; CI, confidence interval; CR, complete remission; D, day; DFCI, Dana-Farber Cancer Institute; CCR, continuous complete remission; DFS, disease-free survival; EFS, event-free survival; HD-MT, high-dose methotrexate; C-MTX, Capizzi methotrexate; HR, high-risk; IDH, Italian, Dutch, Hungarian; IM, intramuscular; IV, intravenous; LBL, lymphoblastic lymphoma; NR, not reported; POG, Pediatric Oncology Group; QOD, every other day; SR, standard-risk; Y, year.

CR rate was 90% with increased CR in the cohort receiving weekly (97%) versus biweekly (82%) dosing, $p=0.003$. Higher CR rate was associated with increased asparaginase activity ($p=0.012$).

The DFCI 91–01 study⁴⁷ assessed intensification of post-remission therapy in patients with newly diagnosed ALL, with the addition of prolonged (30 week) asparaginase administration and dexamethasone in place of prednisone. Furthermore, in addition to randomizations of doxorubicin infusion and cranial radiation dosing, patients were randomized to receive either pegaspargase 2500 IU/m² IM every other week (15 doses) or native *E. coli* asparaginase 25,000 IU/m² IM weekly (30 doses). Patients who received ≥ 26 weeks of L-asparaginase had a 5-year EFS (90%) compared to those who tolerated 25 weeks or less (73%), $p<0.01$. Patients ≥ 9 years were more likely to tolerate <25 weeks ($p<0.01$). Toxicities were more common in older patients (48% for age 9–18 versus 24% for age <9 , $p<0.01$). No statistically significant difference was noted between asparaginase formulations. This protocol was shown to be superior to prior DFCI protocols with improved EFS ($p=0.03$).

Two recent Children's Oncology Group (COG) studies, AALL0232⁴⁸ and AALL0434⁴⁹ yielded differing results when it came to the role of pegaspargase in the interim maintenance phase of their backbone for patients with either B-ALL or T-ALL, respectively. Both compared high-dose methotrexate (HD-MTX; 2–5 g/m² administered over 24 hours with leucovorin rescue) versus the Capizzi regimen (C-MTX) of dose-escalated MTX (100–300 mg/m²) plus pegaspargase during interim maintenance. Five-year EFS was higher for patients receiving HD-MTX versus C-MTX in AALL0232, with the opposite findings in AALL0434. In contrast to the AALL0232 study, fewer relapses were noted in the AALL0434 C-MTX group (32) versus the HD-MTX group (59), including fewer CNS relapses (6 versus 23, respectively). As described above, since pegaspargase itself does not exhibit CNS penetration, this finding was attributed to increased asparagine depletion in patients receiving C-MTX given the two additional cycles of pegaspargase received by this cohort during interim maintenance, though these results may be confounded by differences in timing of cranial radiation in the two studies.

Evidence for Treatment of Adult ALL with Pediatric or Pediatric-Inspired Regimens

Despite this evolution in pediatric ALL care over the course of several decades, progress for adults with ALL has lagged. Several retrospective analyses were performed to assess why despite achieving similar CR rates, outcomes for AYA and adult ALL were inferior to those of pediatric patients. One relatively consistent conclusion was that AYA treated on pediatric studies (many of which utilize more intense administration of asparaginase) fared better, suggesting that this subset of patients is generally better served with these treatment approaches.

A retrospective analysis² of adolescents undergoing treatment in the pediatric FRALLE-93 and adult LALA-94 trials demonstrated improved outcomes with patients treated on the pediatric protocol with CR of 94% versus 83% ($p=0.04$) and estimated 5-year EFS 57% versus 41% ($p<0.0001$). de Bont and others retrospectively assessed adolescent patients treated in the Netherlands on either the pediatric Dutch Childhood Oncology Group (DCOG) or adult Dutch-Belgian Hemato-Oncology Cooperative Study Group (HOVON) treatment protocols.³ They noted a 35% higher 5-year probability of survival for those treated on the pediatric protocol and improved 5-year EFS (69% versus 34%, $p=0.0001$). These findings were attributed to both lower relapse rates and treatment-related mortality rates in the pediatric protocol cohorts. They speculate that key differences between the protocols may have contributed, including the inclusion of reinduction/intensification and maintenance phases in the pediatric protocols, shortened interval between pediatric courses, and absence of methotrexate and increased frequency of allogeneic transplant in the adult protocols.

A retrospective analysis of AYA with newly diagnosed ALL treated with pediatric protocols on consecutive trials in the CCG or the Cancer and Leukemia Group B (CALGB)⁷ also noted similar findings. Despite similar CR rates of 90% between the two groups, 7-year EFS was 63% in the CCG group versus 34% in the CALGB group ($p<0.001$ with relative HR 2.2). OS at 7 years was 67% versus 46% ($p<0.001$ with relative HR 1.9). A meta-analysis⁵⁰ conducted in 2012 included the above trials as well as eight additional comparative studies with a total of 2489 AYA patients treated with either pediatric-inspired or conventional adult regimens. This study demonstrated a lower 3-year all-cause mortality rate

in the pediatric-inspired regimen cohort (relative risk (RR) 0.58) as well as a higher CR rate (RR 1.05), longer EFS (RR 1.66), and lower relapse rate (RR 0.51).

Prospective Studies with Asparaginase in AYA and Adult ALL

Again, early setbacks due to asparaginase-related toxicity in adults limited its use to the pediatric and adolescent population. However, beginning in the 1990s, several studies reassessed its use in the AYA and adult population. Key characteristics and findings from selected trials are summarized in Table 3.

The PETHEMA ALL-96⁶ study was one of the first prospective studies to demonstrate similar response and tolerability to a pediatric regimen in AYA patients. Adolescents (ages 15–18) and young adults (ages 19–30) with standard-risk ALL were enrolled. *E. coli* asparaginase was administered in induction, consolidation, and maintenance cycles with a cumulative dose of 320,000 U/m². Overall CR rate was 98% and OS was 61%, without significant difference in the latter between adolescents (77%) and young adults (63%, $p=0.44$). Of note, 8% developed hypersensitivity reactions to asparaginase requiring treatment interruption, with dose modifications more commonly required in young adults (33% of cycles) versus adolescents (19%, $p=0.03$). The trial also assessed a cohort of older patients (ages 56–77) on the same regimen. CR was achieved in 57.6%, with a high rate of early death (36.4%). This prompted removal of asparaginase and cyclophosphamide from induction, which subsequently improved survival from 20% to 52%.

The HOVON 70 study⁵¹ utilized the FRALLE pediatric approach in previously untreated high-risk adult ALL (ages 17–40). *E. coli* asparaginase (6000 IU/m²) was included in remission induction and intensification cycles. Allogeneic hematopoietic cell transplantation (HCT) was offered to standard- and high-risk patients. Overall CR rate was 91%, 24-month EFS 66%, and OS 72%. These results were improved compared to outcomes from prior HOVON studies, suggesting the feasibility and efficacy of such a regimen in the AYA population.

Several studies included adult patients in addition to AYA. The Group of Research on ALL (GRAALL) 2003 study⁵² assessed a pediatric-inspired ALL regimen in AYA and adult patients (15–60 years) with Philadelphia chromosome (Ph) negative ALL. Patients received multiphase, multiagent chemotherapy with *E. coli* L-asparaginase administered during remission induction, late-intensification, and consolidation. Allogeneic HCT was offered to high-risk patients in first CR. CR rate was 93.5% with EFS 55% and OS 60%. Results from this trial were retrospectively compared to historical data from the LALA-94 trial,⁵³ demonstrating significant improvement in CR, EFS, and OS. Notably, when comparing older (>45 years) versus younger patients, there was a higher cumulative incidence of treatment-related death (23% versus 5%, $p<0.001$) and higher rate of death in CR (22% versus 5%, $p<0.001$), suggesting the need for dose adjustment or alternative approaches in older patients.

The GRAALL-2005 study⁵⁴ was a larger-scale study built on GRAALL-2003, enrolling patients up to 59 years old. Patients received *E. coli* asparaginase for a cumulative planned dose of 48,000 IU/m² during first induction and late intensification phases. Overall CR was 91.9%, with 5-year OS of 52.5% and EFS of 52.2%. Notably, patients ≥ 55 years old fared poorly, with lower 5-year EFS (25.8% versus 55.7%) owing to decreased tolerance of and poorer compliance to planned chemotherapy. Median cumulative dose of L-asparaginase received was greater in patients aged 18–54 compared to those 55 or older (48,000 versus 36,000 IU/m², $p<0.001$). This study did identify a higher best prognostic age cutoff (55) compared to GRAALL-2003 (45), owing in part to differences in sample sizes and presumably increased physician experience with the administration of such regimens in older patients. A single institution study⁵⁵ in adults (18–60) assessed a modified version of the DFCI 91–01 protocol including L-asparaginase during induction and 30 weeks of high-dose L-asparaginase (12,500 IU/m²) during intensification with induction CR of 89%, 5Y OS 63%, and RFS 71%.

Next, several studies assessed pegaspargase in AYA or adult patients in lieu of or in comparison to native L-asparaginase. The German Multicenter Study Group for Adult ALL (GMALL) protocols are pediatric-inspired regimens based on prior BFM protocols optimized for adults. Gökbuget reported⁵⁶ on the results of AYA patients (ages 15–35) in two consecutive studies, GMALL 05/93 and 07/03, with the latter implementing refinements to the protocol, including pegaspargase instead of native L-asparaginase. Improved outcomes were noted in the latter trial, attributed to intensification of treatment, with CR rate increased from 88% to 91% ($p=0.001$) and OS from 46% to 65% ($p<0.0001$).

In the CALGB 9511 study,⁵⁷ Wetzler et al assessed outcomes in patients receiving pegaspargase in lieu of native L-asparaginase in adults. Patients received pegaspargase at 2000 U/m² subcutaneously (3750 U maximum) during

Table 3 Selected AYA and Adult Studies Utilizing Asparaginase-Containing Pediatric or Pediatric-Inspired Regimens

Study (Design)	Enrollment Period	Age Range	Number (Evaluable)	Disease (Status)	Asparaginase Formulation	Treatment Phase and Dosing	Selected Outcomes	Selected Events Including Asparaginase-Related Toxicities
PETHEMA ALL-96 (Non-randomized prospective)	1996–2005	15–30	87 (81)	SR ALL (untreated)	Native <i>E. coli</i>	Induction 10,000 IU/m ² IV D10–12, 17–19, 24–26 Consolidation/Reinduction 10,000 IU/m ² IM/IV D1–3, 15–17 Maintenance/Reinduction 20,000 IU/m ² IV D1 monthly x 12 (cumulative 320,000 U/m ²)	Full cohort: CR: 98% 6Y EFS: 61% (95% CI 51–72%) 6Y OS: 69% (95% CI 59–81%) Young adult versus adolescent: 6Y EFS: 63% (95% CI 48–78) vs 60% (95% CI 43–77), p = 0.97 6Y OS: 63% (95% CI 46–80) vs 77% (95% CI 63–90), p = 0.44	Hypersensitivity – 7 (8%) Dose modifications (vincristine or asp): 19% of cycles (total) 15% of cycles (adolescents) 33% of cycles (young adults) p = 0.03
HOVON-70 (Non-randomized prospective)	2005–2007	17–40	54 (54)	ALL (untreated)	Native <i>E. coli</i>	Induction 6000 IU/m ² IV D8, 10, 12, 20, 22, 24, 26, 28 Intensification 6000 IU/m ² IV D4, 6, 8, 10, 12, 15	CR 91% 24 mo EFS 66% (95% CI 52–77%) 24 mo OS 72% (95% CI 55–82%)	Hypersensitivity – 10 Grade ≥ 3 liver dysfunction – 45 Grade ≥ 3 thrombosis – 9
GRAALL 2003 (Non-randomized prospective)	2003–2005	15–60	225 (225)	Ph-negative ALL (untreated)	Native <i>E. coli</i>	Induction 6000 IU/m ² IV D8, 10, 12, 15, 17, 19, 22, 24, 26 Consolidation 10,000 IU/m ² IV D3 Intensification 6000 IU/m ² IV D8, 10, 12, 20, 22	CR 93.5% 42 mo EFS 55% (95% CI 48–52%) 42 mo OS 60% (95% CI 53–66%) 42 month OS: 66% (age ≤45) vs 41% (age >45) Hazard ratio 2.2 (95% CI 1.4–3.4), p < 0.001	Age 15–45 vs 46–60 Median asp doses (U/m ²) received: Induction: 48,000 vs 36,000 (p=0.006) Postremission: 81,000 vs 29,000 (p=0.003) Allergy or pancreatitis Induction: 2 vs 2 (p = 0.24) Post-remission: 5 vs 4 (p = 0.21) Liver toxicity Induction: 31 vs 15 (p = 0.12) Postremission: 27 vs 9 (p = 0.64) Cumulative incidence of treatment-related deaths: 23% (age >45) vs 5% (age ≤ 45), p < 0.001
GRAAL 2005 (Randomized prospective)	2006–2014	18–59	813 (787)	Ph-negative ALL (untreated)	Native <i>E. coli</i>	Induction and Late Intensification 6000 IU/m ² IV D8, 10, 12, 20, 22, 24, 26, 28 Consolidation 10,000 IU/m ² IV D3, D16 Interphase 10,000 IU/m ² IV D2	CR 91.9% 5Y OS 52.5% (95% CI 48.5–55.7%) 5Y EFS 52.2% (95% CI 48.5–55.7%) 5Y EFS 25.8% (age ≥ 55) vs 55.7% (age < 55), hazard ratio 2.16, p<0.001	Cumulative asp (IU/m ²) actually received: Induction: 48,000 (age 18–54) vs 36,000 (age ≥55) p < 0.001 Late intensification: 48,000 (age 18–54) vs 36,000 (age ≥55) p < 0.150

GMALL 05/93 07/03 (Non-randomized prospective)	NR	15–35	3060 - total (642–05/93) (887–07/03)	ALL (untreated)	Native <i>E. coli</i> (05/93) Pegaspargase (07/03)	Induction 5000 IU/m ² IV D15–28 QOD (05/93) 2000 U/m ² IV D20 (07/03) Consolidation 10,000 IU/m ² IV D2, 16 (05/93) 2000 U/m ² IV D20 (07/03)	CR 91% vs 88% (07/93 vs 05/93), p = 0.001 OS 65% vs 46% (07/93 vs 05/93), p < 0.0001	NR
CALGB 9511 (Non-randomized prospective)	1995–1997	17–71	104 (102)	ALL or AUL (untreated)	Pegaspargase	Induction 2000 IU/m ² (3750 IU cap) D5, 22 Intensification Day 15, 43 *First 21 patients received only one dose during each phase	CR 77% (overall) Asparagine depleted versus non- depleted: CR: 87% vs 73%, p = 0.113 DFS (25 mo vs 12 mo), p = 0.010 HR 1.8 (95% CI 0.9–3.6, p = 0.084) Median OS: 31 mo vs 13 mo, p = 0.001 HR 1.8 (95% CI 1.0–3.2, p = 0.056)	Elevated bilirubin – 54% Hyperglycemia – 40% Hypofibrinogenemia – 30%
DCFI 01–175 (Non-randomized prospective)	2002–2008	18–50	100 (92)	ALL (untreated)	Native <i>E. coli</i>	Induction 25,000 IU/m ² IM D5 Intensification 12,500 IU/m ² IM weekly for 30 weeks with pharmacokinetic dose adjustment	CR 85% 4Y DFS 69% (95% CI 56–78%) 4Y OS 67% (95% CI 56–76%)	Hepatic toxicity – 33 (53%) Hyperbilirubinemia – 10 (11%) Elevated transaminases – 20 (22%) Liver dysfunction or failure – 3 (3%) Thrombosis – 16 (17%) Pancreatitis – 10 (11%) Osteonecrosis – 5 (5%) Allergic reactions – 5 (5%)
NOPHO ALL2008 (Randomized prospective)	2008–2014	1–45	1591 (1509)	Ph- negative ALL (untreated)	Pegaspargase	SR, IR: Consolidation 1000 IU/m ² IM D30, 43, 57, 71, 85 Intensification and Maintenance 1000 IU/m ² IM D99, 113, 127, 141, every 2 weeks from week 23–33 HR: Consolidation 1000 IU/m ² IM D6 Intensification 1000 IU/m ² IM D7, then D1, 15 during week 99–104	EFS 89%, 80%, 74% (age 1–9, 10– 17, and 18–45)	Anaphylaxis 14.5%, 9.5%, 5.2% (age 1–9, 10–17, and 18–45) Pancreatitis 5.9%, 11.1%, 11.3% (age 1–9, 10–17, and 18–45) Hyperlipidemia 7.1%, 9.9%, 7.1% (age 1–9, 10–17, and 18–45) Thrombosis 3.6%, 15.3%, 17.5% (age 1–9, 10–17, and 18–45) Osteonecrosis 2.3%, 13.4%, 8.5% (age 1–9, 10–17, and 18–45)

(Continued)

Table 3 (Continued).

Study (Design)	Enrollment Period	Age Range	Number (Evaluable)	Disease (Status)	Asparaginase Formulation	Treatment Phase and Dosing	Selected Outcomes	Selected Events Including Asparagine-Related Toxicities
CALGB I0403 (Non-randomized prospective)	2007–2018	17–39	318 (295)	Ph-negative ALL (untreated)	Pegaspargase	Induction 2500 IU/m ² IM/IV D4 Remission Consolidation 2500 IU/m ² IM/IV D15, 43 Interim Maintenance 2500 IU/m ² IM/IV D2, 22 Delayed Intensification 2500 IU/m ² IM/IV D4, 5, or 6 and 43	Median OS: NR Estimated 3Y OS: 73% (95% CI 68–78%) 3Y EFS: 59% (95% CI 54–65%) median EFS: 78.1 mo (95% CI 41.8 – NR)	hypofibrinogenemia – 42% hyperglycemia – 30% elevated transaminases – 28% bilirubinemia – 18% hypertriglyceridemia – 11% thrombotic events – 5% pancreatitis – 5% osteonecrosis – 4%
UKALL14 (Non-randomized prospective)	2014–2017	18–60	43 (39)	Ph-negative ALL or LBL (untreated)	Pegaspargase	Induction Phase I and II 2000 IU/m ² IV D15 Intensification I and II 2000 IU/m ² IV D16, 17 Reinduction I and II 2000 IU/m ² IV D15	CR: 97% MRD negativity rate: 33% (post-induction I) 83% (post-induction II) 3Y EFS: 67.8% 3Y OS: 76.4%	Hypofibrinogenemia – 59% Hypertriglyceridemia – 59% Elevated ALT – 41% Hyperglycemia – 31% Elevated AST – 26% Hyperbilirubinemia – 26% Elevated alkaline phosphatase – 10% Hypoalbuminemia – 10% Pancreatitis – 3% Thrombosis – 3%
MDACC ABFM vs HyperCVAD (Non-randomized prospective)	2006–2012	12–40	85 (85)	Ph-negative ALL (untreated)	Pegaspargase	Induction 2500 IU/m ² D4 Consolidation 1 2500 IU/m ² week 3 and 4 Consolidation 2 2500 IU/m ² Week 1 and 4 Consolidation 3A 2500 IU/m ² Week 1 Consolidation 3B 2500 IU/m ² Week 3	CR 94% ABFM vs hyperCVAD 3Y CRD: 70% vs 66% 3Y OS 74% vs 71%	Hepatotoxicity – 35–39% Thrombosis – 22% Pancreatitis – 11% Osteonecrosis – 11%

Note: References: 6, 50, 51, 53, 55, 56, 57, 58, 59, 61, 62.

Abbreviations: ABFM, Augmented Berlin-Frankfurt-Münster; CALGB, Cancer and Leukemia Group B; CR, complete remission; CRD, complete remission duration; D, treatment day; DFS, disease-free survival; DFCI, Dana-Farber Cancer Institute; EFS, event-free survival; GRAALL, Group of Research on ALL; GMALL, German Multicenter Study Group for Adult; HOVON, Dutch-Belgian Hemato-Oncology Cooperative Study Group; HR, high-risk; HyperCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine; IM, intramuscular; IR, intermediate-risk; IV, intravenous; MDACC, MD, Anderson Cancer Center; MRD, minimal residual disease; mo, month; NOPHO, Nordic Society of Pediatric Hematology and Oncology; NR, not reported; PETHEMA, Programa Español de Tratamiento en Hematología; Ph, Philadelphia chromosome; SR, standard-risk; UKALL, United Kingdom ALL.

induction and early intensification courses. Asparagine depletion was defined by SAA >0.03 U/mL for 14 consecutive days following administration. Inferior OS and DFS were noted for patients not achieving depletion, with adjusted HR 1.8 and 1.8, respectively.

DeAngelo reported⁵⁸ on the treatment adult patients (ages 18–50) with newly diagnosed ALL (including Ph-positive disease) in a multicenter study treated with the DFCI 01–175 protocol. Patients received *E. coli* L-asparaginase initially at a single 25,000 IU/m² dose during induction, with additional doses during consolidation pharmacokinetically dose-adjusted based on SAA. Patients with persistently low SAA were switched to pegaspargase or *Erwinia* asparaginase. CR following 1 month of induction therapy was 85%, with 4-year DFS 69% and OS 67%. A 72% of patients were able to receive at least 26 doses, and asparaginase-related toxicities were similar in incidence to those reported in older children.

The Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008 study⁵⁹ assessed a pediatric regimen in patients (ages 1–45) with Ph-negative ALL, with treatment protocol unmodified based on age. Patients first received induction chemotherapy including steroids and multiagent chemotherapy. They were then risk-stratified to receive further treatment with either standard ALL post-induction therapy with delayed intensifications and maintenance or multiple intensive ALL blocks in addition to delayed intensification and maintenance. Regardless of risk, all patients received pegaspargase, high-dose methotrexate, and mercaptopurine, though pediatric patients received pegaspargase at 1000 IU/m² randomized at 2 or 6-week intervals. EFS rates were 89%, 80%, and 74% for ages 1–9, 10–17, and 18–45, respectively. While most treatment-related toxicities in this study were not affected by age, increased frequency of thrombosis, pancreatitis, and osteonecrosis was associated with age >10 , with similar incidence between adolescents and adults.

The Cancer and Leukemia Group B (CALGB) 10403 study⁶⁰ was a prospective trial studying the efficacy of a pediatric regimen in AYA (ages 17–39) with newly diagnosed Ph-negative ALL. The treatment regimen replicated one arm of the COG AALL0232 study with pegaspargase (2500 IU/m² intramuscular [IM] or intravenous [IV]) administered during all courses of treatment except for the final maintenance course. HCT was at the discretion of the treating physician (except those with t(4;11), who received HCT in first CR). Median OS was not reached after a median follow-up of 64 months, with estimated 3-year OS 73%, 3-year EFS 59%, and median EFS 78.1 months. The regimen was well tolerated, with treatment-related deaths in 3%. Asparaginase-associated toxicities were similar to prior studies. Overall, this study demonstrated the efficacy of an intensive pediatric regimen in patients up to 40 years, with improved outcomes (compared to 3-year OS 55% in earlier CALGB studies of this age group) and a relatively low treatment-related mortality. Of note, there were increased rates of hepatic and thrombotic events compared to patients enrolled in the AALL0232 study, with obesity as a risk factor for worse outcomes.⁶¹

The United Kingdom ALL UKALL14 study⁶² utilized a pediatric-inspired regimen in adults (ages 20–60) with untreated ALL or LBL. CR/CRi rate of 97% was achieved with 3-year EFS and OS of 67.8% and 76.4%. Notably, the study included 6 doses of pegaspargase 2000 IU/m² administered in a synchronized manner to avoid concurrent toxicity with other regimen constituents. High-grade asparaginase-related toxicities occurred with increased frequency those age 40–60.

One notable exception among these different treatment regimens is hyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine), which is unique in that it does not include asparaginase. While there has not yet been a head-to-head comparison with hyperCVAD, Rytting reported results from a prospective study of an augmented BFM regimen in AYA with Ph-ALL and compared them to a historical cohort of similar patients given hyperCVAD.⁶³ Overall, they found very similar outcomes in terms of 3-year OS (74% vs 71%) and complete remission duration (70% vs 66%) between the augmented BFM and hyperCVAD groups, respectively. Many skeptics of pediatric-inspired therapy for young adults will cite these data, and though not a prospective randomized trial, they are compelling. That said, one interesting caveat to this analysis pertains to the use of rituximab: Over half of the patients treated with hyperCVAD had CD20+ disease and thus were given rituximab, based on this group's prior experience,⁶⁴ whereas none of the patients treated with augmented BFM received the monoclonal antibody due to paucity of evidence for rituximab use in that patient population at the time. Given that rituximab use has since been validated by a randomized study to yield superior

outcomes when added to a pediatric-inspired regimen for adults with CD20+ B-ALL,⁶⁵ one must consider how the outcomes may have differed had the use of rituximab been consistent between both arms.

Asparaginase Toxicities and Management

Asparaginase has a unique side-effect profile (Figure 1). Given its rare use outside of the treatment of ALL and (until relatively recently) the pediatric population, many adult oncologists encounter difficulties in the management of treatment-related toxicities. This can lead to poor outcomes due to treatment- or disease-related morbidity and mortality, the latter stemming from inappropriate dosing changes or early discontinuation. An expert panel developed recommendations⁶⁶ in 2011 for the management of asparaginase-related toxicities, which have since been incorporated into the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines,⁶⁷ and have been revisited in more recent years given its increasing use in the AYA and adult population.^{68–70} We review these here (with management recommendations summarized in Table 4).

Hepatic Toxicity

Hepatic toxicity includes the most common significant asparaginase-associated adverse events, with high-grade events occurring in up to 50% of adult cases.^{60,71} These can manifest in a broad range of signs and symptoms, from laboratory elevations of transaminases, alkaline phosphatase, and/or bilirubin to synthetic dysfunction leading to hypoalbuminemia, hypofibrinogenemia, or coagulation factor deficiencies. Hepatic toxicity is almost always reversible, and more severe complications are relatively rare. Overt liver failure occurred in 1% of patients in the CALGB 10403 study⁶⁰ and veno-occlusive disease was noted in <1% in ALL2008⁵⁹ trial. Though rare, the incidence of acute liver failure has been linked to other factors or comorbidities, including age and obesity.⁷¹ Hepatic toxicity appears to be dose-dependent and has a typical onset of 2–3 weeks following administration. Although it is almost always reversible, prolonged resolution (>30 days) has been observed.⁷² The underlying mechanism is unclear, though some⁷³ have implicated increased mitochondrial stress and alterations in lipoprotein metabolism due to asparagine/glutamine depletion.

Given the reversibility, management typically involves pausing asparaginase pending resolution, depending on the toxicity grade. Discontinuation is not usually recommended, nor is there evidence to change formulation.^{68–70} Dose reduction can be considered given the propensity of prolonged bilirubinemia, to minimize treatment delays. Prevention strategies are aimed at mitigating risk factors. Dose reduction in patients with risk factors such as obesity can be considered. There is evidence^{74–80} from case reports and series for the use of L-carnitine (with or without B-complex vitamins) and ursodiol for prophylaxis or treatment. A prospective trial (NCT03564678) is currently ongoing to assess the benefits of L-carnitine and vitamin B complex in the treatment of pegaspargase hepatotoxicity.

Hyperammonemia

Ammonia is generated as a byproduct of asparaginase activity and hyperammonemia should be considered in patients who develop extreme fatigue (“asparaginase blues”) or encephalopathy during treatment; and this has been reported in both pediatric^{81,82} and adult^{81,83} populations, though the correlation between hyperammonemia and central neurotoxicity is not entirely clear.⁸² Additional symptoms include headache, nausea, and rash and can be difficult to differentiate from infusion reactions.⁸⁴ Measurement of serum ammonia levels following a suspected infusion reaction may be beneficial to clarify the underlying etiology. Management includes administration of lactulose and supportive care.

Hyperglycemia

Hyperglycemia is commonly seen in both pediatric and adult patients treated with asparaginase, with an all-grade incidence of >90% and up to one-third of patients experiencing grade ≥ 3 . Risk factors include obesity and prior history of diabetes mellitus, both of which are common in the adult population, as well as concomitant use of steroids, which is typical of most asparaginase-containing regimens. Insulin production may also be diminished in the setting of asparagine depletion or pancreatitis, resulting in elevated glucose. Uncontrolled hyperglycemia can lead to complications including diabetic ketoacidosis. Management includes insulin therapy to achieve glycemic control and holding glucocorticoids and asparaginase temporarily for high-grade toxicity.

Hypersensitivity Reactions

Asparaginase is foreign to humans, and hypersensitivity reactions have been noted since its initial use.¹⁵ Current formulations differ in their immunogenicity. Prior to the development of pegylated asparaginase, up to one-third of patients developed hypersensitivity reactions to native *E. coli* asparaginase. Allergic reactions to pegaspargase occur in up to 22% of adults,⁶⁸ with up to 10% of patients experiencing grade ≥ 3 reactions. Route of administration (IM versus IV) appeared to affect rates of high-grade hypersensitivity reactions,⁸⁵ though other studies have not demonstrated such a significant difference.⁸⁶ In studies of calaspargase pegol, hypersensitivity reactions were noted in up to 27%.^{36,87} The safety of *Erwinia*-derived asparaginase following hypersensitivity to other forms of L-asparaginase has been demonstrated,^{88,89} with little cross reactivity between products of different bacterial species.

In adults, premedication is now routinely administered based on data from CALGB 10403, which noted a decrease in the incidence of hypersensitivity reactions from 10% to 4% following a protocol amendment to premedicate asparaginase administration with acetaminophen, diphenhydramine, and hydrocortisone. Similar results have been noted in the pediatric population⁹⁰ and were deemed to be cost-effective.⁹¹

Because asparaginase hypersensitivity is often associated with activity-neutralizing antibodies, recognition and mitigation is critical to ensure that therapeutic efficacy is not impacted. Multiple studies have clearly established inferior outcomes with early discontinuation or dose reduction. This can be challenging, as transient infusion reactions may mimic low-grade hypersensitivity reactions, and the use of premedication may mask a reaction that would signify the development of neutralizing antibodies. "Silent inactivation" of asparaginase can occur in the absence of detectable antibodies or clinical hypersensitivity. While there is evidence that therapeutic drug monitoring (TDM) can be beneficial in these settings, no standard algorithm for TDM exists at this time, and its use has generally been limited to the context of clinical trials.

Management involves the use of premedication for low-grade reactions (with consideration of TDM⁹²) and discontinuation of the offending asparaginase product for high-grade allergic or anaphylactic events with transition to *Erwinia* asparaginase.

Hypertriglyceridemia

There is significant variability in the incidence of hypertriglyceridemia in patients treated with asparaginase, with up to 18% incidence in pediatric and AYA patients⁶⁹ and greater than 50% in adult patients.^{71,93} Formulation-dependent effects have been noted, with patients receiving pegaspargase in the Total XVI trial⁹⁴ having higher incidence of grade 4 hypertriglyceridemia compared to those in the Total XV trial receiving native *E. coli* L-asparaginase (10.5% versus 5.5%, $p=0.007$). Notably, a subset of patients receiving *Erwinia* asparaginase in the Total XVI trial did not develop grade 4 hypertriglyceridemia.⁸² There was no association between hypertriglyceridemia and pancreatitis found in these studies. Because triglyceride levels often resolve to baseline without medical intervention, asparaginase can be continued without dose modification, with consideration of fibrates for high-grade toxicity.

Coagulopathies and Thromboses

Asparaginase-associated coagulopathies are thought to occur through pleiotropic effects on the coagulation and fibrinolytic pathways. Asparagine depletion leads to decreased serum levels of protein C, protein S, plasminogen, antithrombin (AT), and fibrinogen. This can be exacerbated by synthetic dysfunction due to hepatotoxicity. Concomitant use of corticosteroids also contributes through inhibition of fibrinolysis and increased levels of von Willebrand factor, factor VIII, and plasminogen activator inhibitor-1.⁶⁸ The incidence is age-dependent, with other risk factors including obesity, lower white blood cell counts, or mediastinal mass at diagnosis.⁶⁸ The incidence of thrombotic events in the pediatric population is $\leq 5\%$ based on DCFI clinical trials.

Lower-limb and catheter-associated venous thromboembolism (VTE) are the most common, though other life-threatening events such as pulmonary embolism (PE), arterial thromboembolism, and cavernous sinus thromboses (CST) can occur. The latter is often associated with intracranial hemorrhage. Thrombotic events tend to occur earlier

Table 4 Selected Asparaginase Associated Toxicities and Their Management

Toxicity	Incidence – n (%) – Grade ≥ 3 Unless Specified	Management Recommendations
Hypersensitivity	CALGB 10403–29 (9.8) NOPHO2008 – 11 (5.2) UKALL14 – 3 (4) DFCI – 5 (5)	NCCN: Grade ≤ 2 allergy: continue same asparaginase formulation with addition of premedication, reduction of infusion rate, or concurrent saline administration. Grade ≥ 3 allergy or anaphylaxis: permanently discontinue offending formulation. <i>Erwinia</i> asparaginase should be used in the second-line. Additional/alternative recommendations based on expert opinion: For grade 1 reactions, SAA should be measured within 3–7 days of asparaginase administration with a therapeutic trough ≥ 0.1 IU/mL to ensure adequate anti-leukemic activity. Transition to <i>Erwinia</i> asparaginase for subtherapeutic level or recheck at day 14 and transition at that point. Some experts recommend switching asparaginase preparations with grade ≥ 2 allergy.
Elevated transaminases	CALGB 10403 ALT – 158 (53.6) AST – 98 (33.2) NOPHO2008 – NR UKALL14 ALT – 10 (14) AST – 4 (5) ALP – 15 (20) DFCI – 20 (22) (AST or ALT)	NCCN: Grade 3: Hold asparaginase until grade 1, then resume; Grade 4: Hold asparaginase until grade 1, then resume. Consider discontinuation or resumption with close monitoring if > 1 week to resolution. Additional expert recommendations: Discontinuation of asparaginase is not recommended due to reversibility of hepatotoxicity and impaired outcomes with undertreatment.
Hyperbilirubinemia	CALGB 10403–77 (26.1) NOPHO2008 – 5 (2.4) (bilirubin > 5 x ULN or encephalopathy) UKALL14 – 17 (23) DFCI – 10 (11)	NCCN: Continue asparaginase for direct bilirubin ≤ 3.0 mg/dL. Hold for 3.1–5.0 mg/dL until < 2.0 mg/dL. For > 5.0 mg/dL, discontinue asparaginase or hold and resume when < 2.0 mg/dL with close monitoring and consideration of dose reduction
Hyperlipidemia / hypertriglyceridemia	CALGB 10403–33 (11.2) NOPHO2008 – 15 (7.1) (> 5 ULN) UKALL14 – 1 (1) DFCI – NR	NCCN: Grade 4: hold asparaginase and resume when normalized. Treat as indicated. Additional expert recommendations: Several experts recommend treatment with gemfibrozil or other fibrates, particularly for high-grade triglyceridemia (>1000 mg/dL), though the benefits are unclear. Most experts recommend continuing asparaginase without interruption or dose adjustment regardless of grade.
Pancreatitis	CALGB 10403–14 (4.7) NOPHO2008 – 24 (11.3) (Grade ≥ 2) UKALL14 – 2 (3) DFCI – 10 (11)	NCCN: Grade 2: hold asparaginase until enzyme levels or radiologic findings resolve. Grade ≥ 3: permanently discontinue asparaginase
Hyperglycemia	CALGB 10403–35 (11.9) NOPHO2008 - NR UKALL14 – 0 (0) DFCI – 41 (45)	NCCN: Continue asparaginase for grade ≤ 2 toxicity and hold asparaginase and glucocorticoids for grade ≥ 3 toxicity. Insulin therapy should be initiated to achieve glycemic control.

(Continued)

Table 4 (Continued).

Toxicity	Incidence – n (%) – Grade ≥ 3 Unless Specified	Management Recommendations
Thrombosis	CALGB 10403–33 (11.2) NOPHO2008 – 37 (17.5) UKALL14 – 4 (5) DFCI – 16 (17)	NCCN: For grade ≥ 2 non-CNS thromboembolism, systemic anticoagulation should be initiated with antithrombotic agent (heparin or low molecular weight heparin). Asparaginase should be held until symptomatic resolution and completion of anticoagulation or stability. AT levels should be tested if heparin is administered. For CNS thrombosis, stroke, or ischemic event, asparaginase should be discontinued and antithrombotic therapy initiated if appropriate. Grade ≤ 3, resumption of asparaginase, with possible dose reduction or greater intervals between doses should be considered. Grade 4: asparaginase should be discontinued permanently. Additional expert recommendations: The use of DOACs is generally not recommended due to limited data. Continue therapeutic anticoagulation for at least 6 months and minimum of 4–6 weeks following asparaginase therapy, with longer duration (through achievement of CR) considered for patients with life threatening VTE. Anti-Xa and AT level monitoring (target 80–120%) is recommended. For life-threatening VTE, consider short-term administration of AT concentrate pending stability. There is limited data for prophylactic anticoagulation with some experts recommending prophylaxis during induction for all patients throughout asparaginase therapy for patients with risk factors (prior VTE, obesity). Cryoprecipitate should not be administered for hypofibrinogenemia in the absence of bleeding due to increased risk of thrombosis.
Hemorrhage	CALGB 10403 (CNS) – 4 (1.4) NOPHO2008 – 11 (5.2) - (CNS or other catastrophic) UKALL14 (CNS) – 1 (1) DFCI (CNS) – 1 (1)	NCCN: For non-CNS Grade ≥ 2: hold asparaginase until Grade 1. Consider coagulation factor replacement. Treatment should not be held for asymptomatic abnormal laboratory findings. For CNS asparaginase should be discontinued and coagulation factor replacement considered. Resumption can be considered for grade ≤ 3 pending resolution with dose reduction or greater intervals between doses but should not be resumed for grade 4. It is recommended that magnetic resonance angiography/venography be performed to assess for associated CST

Notes: References: 65, 66, 67, 68, 84, 87. "Grade" Refers to Common Terminology Criteria for Adverse Events (CTACE) Grade.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AT, anti-thrombin, CALGB, Cancer and Leukemia Group B; CNS, central nervous system; CST, cavernous sinus thrombosis; DFCI, Dana-Farber Cancer Institute; DOAC, direct-acting oral anticoagulant; NCCN, National Comprehensive Cancer Network; NOPHO, Nordic Society of Pediatric Hematology and Oncology; NR, not reported; SAA, serum asparaginase activity; UKALL, United Kingdom Acute Lymphoblastic Leukaemia; ULN, upper limit of normal; VTE, venous thromboembolism.

during therapy, so factors contributing to their development are likely not limited to asparaginase effects: disease-related prothrombotic state, venous catheter placement, and/or steroid administration.⁹⁵

Recommendations for management are similar to that for other VTEs with some special considerations (Table 4). Successful use of direct oral anticoagulants (DOAC) has been reported, though it is currently not recommended for use by some in this setting.⁹⁵ Asparaginase should be held pending stability and discontinued for CST or other grade 4 events. For hemorrhagic events, asparaginase should be held or discontinued depending on location and degree, with consideration of factor replacement.

The role of prophylaxis is less clear. In a retrospective study⁹⁶ of patients treated on DFCI Consortium protocols, VTE occurred in 8% of patients, with higher incidence in adults (34%). The role of VTE prophylaxis in adult patients was assessed⁹⁷ following a protocol amendment to patients treated at DCFI. Two-year cumulative incidence of VTE (41% to 28%) and PE (16% to 8%) both improved, but not with statistical significance. However, bleeding complications were also not significantly increased with the addition of anticoagulation (0% versus 6%, p=0.26). Prophylactic administration of cryoprecipitate is not recommended in the absence of active bleeding due to the increased risk of VTE observed in patients receiving cryoprecipitate in this setting,^{71,95} nor is prophylactic AT replacement.

Pancreatitis

Asparaginase-associated pancreatitis (AAP) has been noted in the earliest studies,^{98–100} however the mechanism remains unclear. Incidence in pediatric patients is up to 18%^{59,63,101} and up to 14% in adults.^{59,60,63,71,102} Several studies have attempted to identify risk factors for development of AAP. One systematic review¹⁰³ identified older age, higher disease-risk stratification, pegaspargase, and dosing as potential risk factors. Multiple studies have identified potential genetic associations,^{104–106} including those already known to be associated with alcohol-induced or idiopathic pancreatitis in adults. Asparaginase should be held pending resolution of asymptomatic (chemical) pancreatitis and should be permanently discontinued for grade ≥ 3 toxicity. Prophylactic use of octreotide in both pediatric and adult patients at risk for AAP may be beneficial,¹⁰⁷ however this is currently not in widespread use.

Future Directions and Ongoing Trials

Novel Asparaginase Formulations

JZP-458

JZP-458 (RylazeTM - Jazz Pharmaceuticals) is a recombinant *Erwinia* asparaginase produced in *Pseudomonas fluorescens* without immunologic cross-reactivity with native asparaginase.³⁰ A randomized, single-center, open-label Phase 1 study in healthy adults¹⁰⁸ demonstrated safety, tolerability, and therapeutic SAA levels when dosed at 25 mg/m² IM and 37.5 m/m² IV on a Monday/Wednesday/Friday schedule. A Phase 2/3 study¹⁰⁹ (NCT04145531) is ongoing in patients with ALL/LBL who experienced hypersensitivity reactions or silent inactivation with *E. coli* asparaginase and at least one treatment course remaining. Each course of asparaginase was substituted with 6 doses of JZP-458 on a Monday/Wednesday/Friday schedule with escalating doses in each cohort. Preliminary data¹¹⁰ demonstrated a positive risk-benefit profile when dosed at 25 mg/m² IM on Monday and Wednesday and 50 mg/m² on Friday with therapeutic SAA levels detected in >90% at 48 and 72 hours post-administration. Grade ≥ 3 all-cause toxicities occurred in 72% of patients with abnormal liver function tests (62%) as the most common all-grade toxicity. Hypersensitivity reactions occurred in 25% (any-grade) and 2% (grade ≥ 3) of patients.

Eryaspase

Eryaspase (GRASPA[®] - Erytech) is a formulation of erythrocyte-encapsulated *E. coli* asparaginase designed to increase its half-life and bioavailability and decrease immunogenicity. Several trials investigated this formulation in pediatric and adult ALL.^{111,112} Among the more definitive studies, the GRASPALL 2009–06 trial¹¹¹ assessed eryaspase combined with multiagent chemotherapy in adult and pediatric patients with relapsed Ph-negative ALL. Patients who had no prior allergy to L-asparaginase were randomized to receive either native asparaginase (10,000 IU/m²) or eryaspase (150 IU/kg); those with prior allergy received eryaspase. Hypersensitivity reactions were less frequent (0% vs 43%, $p < 0.001$) and asparaginase activity maintained for longer (25.5 vs 9.8 days, $p < 0.001$) in the eryaspase cohort. The NOR-GRASPALL 2016 study (NCT03267030) is evaluating eryaspase in combination with multiagent chemotherapy in patients with non-high-risk ALL who develop pegaspargase hypersensitivity. Patients received eryaspase at 150 U/kg to complete asparaginase therapy (1–7 doses). Preliminary data¹¹² demonstrated detectable SAA at expected nadirs 14 days following administration in 94.7% of patients with 90.7% of samples >100 U/L and 69.3% >400 U/L. Adverse events related to eryaspase were noted in 22%, including six patients with a possible allergic reaction and three with low activity.

Calaspargase Pegol

Calaspargase pegol (AsparlasTM - Servier Pharmaceuticals) was FDA approved in 2018, with data from the DCFI 11–001 Phase III trial²³ noting similar outcomes, SAA, and toxicity profile to pegaspargase in patients (ages 1–21) with newly diagnosed ALL or LBL randomized to receive either IV pegaspargase or calaspargase pegol. Given these findings in this population, a multicenter, open-label, single-arm phase 2/3 trial (NCT04817761) is underway, incorporating calaspargase pegol into a COG backbone for adults (ages 22–65) with newly diagnosed Ph-negative ALL.

Asparaginase ± Immunotherapy

Immunotherapeutic approaches targeting leukemic antigens have demonstrated tremendous promise in the treatment of ALL, both in the upfront and relapsed/refractory (R/R) setting, which raises the potential for addition of these agents to multiagent chemotherapy backbones containing asparaginase.

Inotuzumab ozogamicin (InO) is an antibody–drug conjugate consisting of a humanized anti-CD22 IgG4 monoclonal antibody linked to the cytotoxic agent calicheamicin. InO is FDA-approved as monotherapy for R/R B-ALL based on data demonstrating high rates of CR in patients treated with InO compared to salvage chemotherapy alone.^{113,114} The A041501 clinical trial¹¹⁵ (NCT03150693) is a phase III trial combining InO with multiagent chemotherapy similar to the C10403 regimen in AYA patients with newly diagnosed B-ALL. InO is administered on days 1, 8, and 15 during the remission induction phase with a primary outcome measure of EFS.

Blinatumomab is a bispecific T-cell engager targeting CD19 and CD3 approved for R/R B-ALL based on results of the TOWER trial¹¹⁶ and for treatment of MRD based on the BLAST trial.¹¹⁷ Several studies are currently evaluating its efficacy as frontline therapy in both pediatric and adult B-ALL. The AALL1731 trial (NCT03914625) is a Phase 3 study investigating the addition of blinatumomab in between cycles of a standard asparaginase-containing multiagent chemotherapy regimen with primary endpoints of DFS in children and young adults (ages 1–31) with newly diagnosed standard-risk B-ALL, B-ALL associated with Down syndrome, or localized B-LBL.

Both InO and blinatumomab are associated with hepatic toxicity,¹¹⁸ including sinusoidal obstruction syndrome in the case of InO, particularly in those undergoing subsequent HCT. Given the relatively high incidence of hepatotoxicity in patients receiving asparaginase, it will be important to determine whether the combination blinatumomab or InO in regimens containing asparaginase whether administered simultaneous or in sequentially will exacerbate these toxicities.

Asparaginase ± Targeted Agents

Tyrosine kinase inhibitors (TKI) are an essential component of the management of Ph-positive ALL and have been added to intensive regimens containing asparaginase in the pediatric population. Dasatinib in combination with multiagent chemotherapy including asparaginase in the adult population has also been reported. In the EWALL-PH-01 study,¹¹⁹ dasatinib administered in combination with a low-intensity asparaginase-containing regimen in older patients (age≥55) resulted in CR of 96%, 1-year RFS 58%, and 5-year OS 36%. In contrast, significant toxicity was noted in the UKALL14 study using imatinib.¹²⁰ Other targeted agents are also being actively studied in ALL. A phase 1 trial (NCT03571321) is ongoing to assess the benefit of ruxolitinib in combination with multiagent chemotherapy including pegaspargase for AYA with Ph-like ALL who achieved CR following induction chemotherapy.

Therapeutic Drug Monitoring

TDM for serum asparaginase activity is feasible with FDA and CLIA-certified assays currently available, which can be used in the context of concern for silent inactivation or an ambiguous allergic reaction. SAA of ≥0.1 IU/mL has been accepted as a suitable target trough level to ensure clinically efficacious serum asparagine depletion. Given the differing pharmacokinetics of pegaspargase and *Erwinia* asparaginase, experts recommend this trough to be achieved 14 days post-administration for pegaspargase and prior to each dose for *Erwinia* asparaginase.²⁶ The optimal level prior to 14 days is unclear; however, several experts recommend that all patients receiving asparaginase be tested regardless to minimize the possibility of underdosing due to missed silent inactivation with SAA measurement 3–7 days following non-*Erwinia* asparaginase administration and immediate transition to *Erwinia* asparaginase for level <0.1 IU/mL. TDM also offers the possibility of individualized dosing strategies, though this is not done outside of the context of clinical trials. Intriguing recent data from the DCOG ALL-11 study^{121,122} noted that TDM could result in significant dose reductions of pegaspargase with retained therapeutic activity, though notably the effect on toxicity was minimal. Another recent study²⁴ did not note a significant association between overall asparaginase-associated toxicity and SAA, but it did note increased risk of pancreatitis and osteonecrosis with increasing SAA.

Institutional Approach to Use of Asparaginase in Adults with ALL

As we have described, there are many different strategies in which asparaginase can be considered in the management of adult ALL. However, how to implement such approaches optimally remains a subject of some debate. Lacking a uniformly accepted strategy, these are some general principles used at our center when deciding between these many different approaches. They are based on the totality of the literature summarized above, though specific references are cited when appropriate.

In the context of front-line therapy, we primarily reserve the use of pegaspargase for young adults with Ph-negative ALL as part of the C10403 regimen.⁶⁰ For patients with relapsed disease, particularly T-cell ALL and/or with CNS involvement, we may use pediatric salvage regimens like ALL R3¹²³ or POG 9412.¹²⁴ We will generally use these approaches for patients up to age 40, though older age within this range and elevated BMI (particularly over 30 kg/m²) raises concerns for toxicity. One way to potentially mitigate this is to cap doses of pegaspargase (3750 U). We do not use any form of thrombotic prophylaxis. In fact, we typically do not monitor clotting times and fibrinogen levels: they will often be abnormal, enticing practitioners to intervene out of concern for hemorrhagic complication, despite the greater risk of thrombosis.¹²⁵

Our practice surrounding the risk of asparaginase-mediated reactions has varied, in part due to the shifting availability of *Erwinia* asparaginase. As of this writing, we typically provide premedication in the form of acetaminophen, diphenhydramine, and (when not being given as part of the treatment regimen) corticosteroids to prevent infusion-related reactions. The downside of such an approach is that it may increase the risk of silent inactivation. However, this is an uncommon phenomenon, and any adverse reaction regardless of etiology can negatively impact the patient (up to and including refusal to receive subsequent doses). Historically, we have not routinely monitored SAA levels. One reason for this was due to system-based challenges in identifying a reliable laboratory that could perform this assay in a timely fashion. The other (and more important) reason was lack of access to an alternative asparaginase product to use in patients identified as having silent inactivation of pegaspargase. With these issues recently addressed, we are revisiting our approach to this problem. Separately, while strategies to dose-adjust pegaspargase based on SAA results are intellectually appealing, the data supporting such methods are relatively lacking. In the event of an infusion-related reaction, we generally use the timing and nature of symptoms and signs to discriminate between anaphylactoid vs antibody-mediated hypersensitivity reactions.⁸⁴ In cases that are harder to discriminate, we will check a SAA and ammonia levels as soon as feasible. If antibody-mediated neutralization is ultimately suspected, we will then switch to *Erwinia* asparaginase for all subsequent doses. This includes an attempt to make up for the dose impacted by the observed reaction, since the reaction would render that dose inert.

There tends to be less nuance and controversy surrounding management of other adverse events from asparaginase, so our practice typically follows the recommendations and guidelines cited above (Table 4). Despite the limited data,⁷⁴ we have used L-carnitine and vitamin B complex in cases of severe hepatic toxicity (eg, bilirubin >10 mg/dL); our anecdotal experience has been mixed. Since the evidence supporting this strategy is relatively modest (ie, unclear magnitude of benefit and theoretical deleterious impact on therapeutic intent of asparaginase), we have reserved this intervention for the most significant cases of liver injury. In cases of significant hypertriglyceridemia, we typically institute gemfibrozil for the remainder of the asparaginase-containing portion of the treatment, discontinuing this agent once the asparaginase-containing portion of the treatment is complete and fasting lipid levels have improved. VTE is typically managed either with LMWH or DOAC. While the latter have not been studied thoroughly in this specific situation, their safety profile, ease of administration, and mechanism of action make them appealing, particularly since they work independent of antithrombin levels. Similar to gemfibrozil, we typically continue therapeutic anticoagulation for at least as long as the asparaginase-containing treatment, assuming that asparaginase was the inciting event. Clinically significant pancreatitis almost always leads to permanent discontinuation of asparaginase.

Conclusion

Asparaginase has been an essential component of ALL therapy for decades. However, until relatively recently, its use has been limited to the pediatric population. Its success in these patients and several seminal studies demonstrating its potential to improve outcomes in the AYA and adult population has led to its broader use. In these populations, however,

particularly in older adult patients, it is associated with increased morbidity. An understanding of its unique side-effect profile and management is critical to mitigate treatment-related morbidity and to avoid inferior outcomes due to inappropriate dose reduction or cessation. Ongoing areas of investigation include the incorporation of asparaginase into current adult treatment paradigms, combination with immunotherapy or targeted agents, novel formulations, and therapeutic drug monitoring.

Disclosure

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