Blood Reviews 53 (2022) 100908

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/issn/0268960X

Review

Optimizing use of L-asparaginase–based treatment of adults with acute lymphoblastic leukemia

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ARTICLE INFO

Keywords:
Acute lymphoblastic leukemia
Adults
Asparaginase
Efficacy
Safety

ABSTRACT

Acute lymphoblastic leukemia (ALL) is a malignancy of lymphoid progenitor cells occurring at an annual incidence rate of approximately 1.1 to 2.1 per 100,000 person-years globally. Approximately 40% of annual ALL cases occur in adults, yet estimated 5-year overall survival rates are about 40% to 50% in adults (and vary broadly by age) compared with 90% in children. Although the addition and/or intensification of asparaginase as a key treatment strategy for pediatric ALL is well recognized, further research is needed to clarify the benefit/risk ratio in adult patients with ALL. This review emphasizes the importance of efficient management of adverse events to increase asparaginase efficacy and explores novel strategies for optimizing asparaginase treatment, including new formulations of asparaginase, pharmacokinetic-based dosing, and pharmacogenetic profiling. Upcoming results of adult ALL trials should further clarify the role of asparaginase, building on the results of the large NOPHO 2008, CALGB 10403, GRAALL-2005, GMALL 07/2003, and UKALL14 trials.

1. Introduction

Acute lymphoblastic leukemia (ALL) is a malignancy of lymphoid progenitor cells that occurs at an annual incidence rate of approximately 1.1 to 2.1 per 100,000 person-years globally [1]. The most common pediatric cancer in the United States, ALL represents 20% of all cancer cases reported in persons aged <20 years [2,3]. However, the incidence of ALL by age is also bimodal, with peaks occurring at approximately 5 years and at 50 years of age; overall, about 40% of annual ALL cases occur in adults [4,5].

Estimated ALL 5-year overall survival (OS) rates approach 90% in children with the best treatment regimens [6] compared with approximately 40% to 50% in adults, with considerable variation by age, treatment, and other risk factors [4,7]. The high survival rates in children, which represent a significant improvement in ALL pediatric outcomes over the past 40 years, are generally attributed to use of improved, intensified treatment protocols [4,7]. True pediatric or "pediatric-inspired" regimens that are asparaginase intensive are increasingly being used in younger adults, even up to age 50 to 60 years, and have improved survival rates compared to historical controls [7–11]. However, outcomes are also stratified by age within the adult category, with OS declining with increasing age, from as high as 75% in adolescents and young adults (AYA) aged <25 years to only 10% to 20% in those aged >55 years [7,12,13].

Factors proposed to explain the ALL outcomes disparity between children and adults include a high frequency of the favorable cytogenetic abnormalities in children, mostly t(12;21) and hyperdiploidy, which are rarely seen in adults, and higher incidences of immature subtypes, such as early T- and pro-B-ALL [14–16], in children. In addition, researchers have cited less tolerance of intensive chemotherapy among adults, lack of a standardized regimen and prospective data to support one, and lack of experience treating adult ALL [17,18]. However, these factors do not entirely explain the disparity since only a minority of adults have adverse prognostic attributes, and outcomes for adult Philadelphia chromosome positive (Ph+) ALL have improved with use of tyrosine kinase inhibitors (TKIs) [15,19,20].

Intensive use of asparaginase-containing regimens is a key factor contributing to the high survival rates in pediatric ALL [7,10,21,22]. Although the benefits of asparaginase-containing regimens are not as well studied in adults compared with children, the available data

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https://doi.org/10.1016/j.blre.2021.100908

Available online 12 November 2021

Table 1
Outcomes of pediatric-inspired regimens for adult ALL in selected studies [17].

Study	*N*	Median age (range), y	Asparaginase dose/schedule	CR, %	Induction death, *n* (%)	OS, %	DFS/EFS, %
CALGB 10403 [11]	295	24 (17–39)	PEG-ASP, 2500 IU/m^2 (IM or IV), × 1 dose on Day 4 of Induction, Days 15 and 43 of Consolidation, Days 2 and 22 of Interim Maintenance, Days 4 **or** 5 **or** 6 **and** Day 43 of Delayed Intensification, Days 2 and 22 of Interim Maintenance II, Days 4 **or** 5 **or** 6 **and** Day 43 of Delayed Intensification II	NR	9 (3)	3-y = 73	3-y EFS = 59
NOPHO[a] ALL2008 [28]	221	NR (18–45)[b]	PEG-ASP, 1000 IU/m^2 IM, × 1 dose every 2 weeks of Consolidation and Delayed Intensification I periods for standard- and intermediate-risk patients; on 1 day only of each period for high-risk patients	NR	3 (1)	5-y = 78	5-y EFS = 74
GRAALL-2005 [30]	787	36.1 (IQR, 24.8–48.4)	EC-ASP, 6000 IU/m^2 IV, × 1 dose on Days 20, 22, 24, 26, and 28 of Induction and of Intensified Induction; × 1 dose on Days 8, 10, 12, 18, 20, and 22 of Late Intensification	91.9	44 (6)	5-y = 59	5-y EFS = 52
DFCI [31]	92	28 (18–50)	EC-ASP, 25,000 IU/m^2 × 1 dose on Day 5 of Induction; individualized dosing, 12,500 IU/m^2/dose during Intensification (30 weeks); no doses during Maintenance	85	1 (1)	4-y = 67	4-y DFS = 69 4-y EFS = 58
USC [32]	51	32 (18–57)	PEG-ASP, 2000 IU/m^2 IV, at various intervals of ≥4 weeks based on serum asparaginase activity and asparagine depletion	96	1 (2)	7-y = 51	7-y DFS = 58
PETHEMA [33]	126	37.5 (18–60)	EC-ASP, 10,000 IU/m^2 IV, × 1 dose on Days 16–20 and 23–27 and 20,000 IU/m^2 Day 3 of each of 3 Early and Delayed Consolidation cycles **or** PEG-ASP, 2000 IU/m^2 IV, Day 15 for 4 weeks of Induction I and Day 3 of each of 3 Early and Delayed Consolidation cycles Cumulative EC-ASP and PEG-ASP were 220,000 IU/m^2 and 14,000 IU/m^2, respectively; a 50% reduction in the PEG-ASP dose was mandatory in patients aged >50 years, and the PEG-ASP dose was limited to 3750 IU in patients with BSA >1.8 m^2	93	7 (6)	3-y = 60	3-y DFS = 45
HOVON [34]	54	26 (17–39)	EC-ASP, 6000 IU/m^2, × 1 dose starting Days 8, 10, 12, 15, 17, 19, 22, 24, and 26 of Induction; × 1 dose on Days 4, 6, 8, 10, 12, and 15 of Intensification IA; × 1 dose on Days 4, 6, 8, 10, 12, and 15 of Intensification IIA	91	2 (4)	2-y = 72	2-y EFS = 66
FRALLE 2000BT [35]	89	Adolescent: 18 Young adult: 23	EC-ASP, 6000 IU/m^2 IM or IV, × 1 dose on 3–6 days, depending on age and risk stratification, at 2–3-day intervals, during Induction and Intensification periods I and II	99	NR	5-y = 66	5-y EFS = 61
MDACC [36]	106	22 (13–39)	PEG-ASP, 2500 IU/m^2, × 1 dose on Day 4 of Induction and in Weeks 3 and 4 of Consolidation I, Weeks 1 and 4 of Consolidation II, Week 1 of Consolidation IIIA, and Week 3 of Consolidation IIIB [37]	93	1 (1)	5-y = 60	NR
GMALL 07/2003 [38]	1226	35 (15–55)	PEG-ASP, 2000 IU/m^2 IV,[c] × 1 dose on Day 18 of Induction and Days 2 and 16 of Consolidation, with reduced dose in patients aged >55 years [39]	91	(4–5)	3-y = 60–67	NR
MSKCC [29]	39	39 (20–60)	PEG-ASP, 2000 IU/m^2 IV on Day 15 of Induction I and II, Day 16 or 17 of Intensification I and II, and Day 15 of Reinduction I and II	97[d]	0	3-y = 76	3-y EFS = 68

ALL, acute lymphoblastic leukemia; BSA, body surface area; CALGB, Cancer and Leukemia Group B; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; DFCI, Dana-Farber Cancer Institute; DFS, disease-free survival; EC-ASP, ***E. coli***–asparaginase; EFS, event-free survival; FRALLE, French Acute Lymphoblastic Leukemia Group; GMALL, German Multicenter Study Group for Adult ALL; GRAALL, Group of Research on Adult ALL; HOVON, Hemato-Oncologie voor Volwassenen Nederland; IM, intramuscular; IQR, interquartile range; IV, intravenous; MDACC, MD Anderson Cancer Center; MSKCC, Memorial Sloan Kettering Cancer Center; NOPHO, Nordic Society of Pediatric Hematology and Oncology; NR, not reported; OS, overall survival; PEG-ASP, pegaspargase; PETHEMA, Programa Español de Tratamientos en Hematología; USC, University of Southern California.

[a] NOPHO ALL2008 study data given for the for the adult cohort (aged 18–45 years; $n = 221$) only.

[b] Of NOPHO ALL2008 patients ($n = 1509$), 1022 (67.7%) were aged 1 to 9 years; 266 (17.6%) were aged 10 to 17 years; and 221 (14.6%) were aged 18 to 45 years.

[c] The PEG-ASP dose was increased during the study from 1000 IU/m^2, as originally planned, to 2000 IU/m^2 in Induction and from 500 IU/m^2 to 2000 IU/m^2 in Consolidation; this table gives the rates of CR, induction death, and OS for both cohort 1 (treated with PEG-ASP 1000 IU/m^2; $n = 826$) and cohort 2 (treated with PEG-ASP 2000 IU/m^2; $n = 400$).

[d] Value represents CR/CRi rate.

support the use of asparaginase in this population [7,23–25].

There are 3 formulations of asparaginase—native ***Escherichia coli*** (***E. coli***)–asparaginase (EC-ASP), pegylated ***E. coli*** asparaginase (pegaspargase and calaspargase pegol-mknl), and ***Erwinia*** asparaginase (ER-ASP)—which differ in their pharmacokinetics (PK) and tolerability [10,26]. Several toxicities associated with asparaginase (i.e., hepatotoxicity and thrombosis) increase with age [17,27]. This review will discuss the trends and issues associated with asparaginase use in adult ALL and the potential for various measures to minimize the risks and maximize the benefits of asparaginase-based treatment of ALL in adults.

2. Asparaginase for adults with ALL: Current data

Among recent studies using pediatric protocols in adults that include more asparaginase, the Cancer and Leukemia Group B (CALGB) 10403 study in 295 adults with ALL (aged 17–39 years) used a regimen identical to an arm of the Children's Oncology Group (COG) study AALL0232 with seven doses of pegaspargase [11]. Overall treatment-related mortality was 3%, 3-year event-free survival (EFS) was 59% (95% confidence interval [CI]: 54%–65%), the median OS was not reached, and the estimated 3-year OS was 73% (95% CI: 68%–78%) (Table 1). The Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008 study evaluated outcomes with pegaspargase within the same chemotherapy regimen by 3 age groups—1 to 9 years ($n = 1022$), 10 to 17 years ($n = 266$), and 18 to 45 years ($n = 221$)—and stratified by risk categories of standard, intermediate, and high [28]. A recent phase 2 study of a pediatric-inspired pegaspargase regimen in adults aged 18 to 60 years with newly diagnosed ALL/lymphoblastic lymphoma (LBL) showed high minimal residual disease (MRD)–negativity rates and promising survival outcomes [29].

Initial findings from NOPHO showed that patients aged 18 to 45 years had a greater incidence of unfavorable risk factors including T-cell ALL, ***KMT2A-r***, and higher levels of end of induction MRD for B-lineage ALL. Five-year EFS and OS were 85% and 91%, respectively, for the total population, and 74% and 78%, respectively, for the young adult population (Table 1) [11,17,28–39]. However, unfavorable risk factors were significantly associated with worse probable EFS. Toxicity rates were similar between children and adults, except for increased risks of thrombosis, pancreatitis, and osteonecrosis in patients aged ≥10 years versus younger patients ($p < 0.001$ for all), which the investigators considered most likely associated with asparaginase treatment. However, incidence of these adverse events (AEs) did not differ between adolescents and adults [28].

Another recent report from the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL)-2005 study, which used EC-ASP, stated that increasing age was associated with decreased tolerance of the pediatric-inspired protocol and corresponding reductions in complete remission (CR), EFS, and OS, such that an age of 55 years appeared to be the best cutoff for use. Five-year EFS was 55.7% in patients aged <55 years versus 25.8% in those aged ≥55 years [30].

TKIs have become the standard of care in combination with chemotherapy, including regimens containing pegaspargase, in adults with Ph+ ALL [40]. However, it has been suggested that asparaginase treatment-associated hyperbilirubinemia could necessitate interruption of TKI therapy and that this combination should therefore be avoided [41]. Only one study has reported safety outcomes of asparaginase and concomitant dasatinib in adults; of 71 patients, there were five reports of serious transaminase elevations [42].

3. Is asparaginase essential to adult ALL regimens?

The role and importance of asparaginase (including factors of dose, frequency, and duration) and asparagine depletion in adult ALL treatment regimens is another controversial issue that requires further research to clarify the benefit/risk ratio. The CALGB 9511 trial used pegaspargase during induction in adult patients with ALL to determine the relationship between asparaginase depletion and outcomes [23]. Of the 85 eligible patients, 63 achieved asparagine depletion (median age, 32 [range: 17–70] years), and 22 did not (median age, 48 [range 22–71] years). In a univariate analysis, absence of asparagine depletion was associated with inferior OS (hazard ratio [HR]: 2.4, 95% CI: 1.4–4.1; $p = 0.001$) and disease-free survival (DFS; HR: 2.2, 95% CI: 1.2–4.1; $p = 0.010$). After adjustment for age, performance status, white blood cell (WBC) count, and karyotype, the OS HR associated with absence of asparagine depletion was 1.8 (95% CI: 1.0–3.2; $p = 0.056$), and the EFS HR was also 1.8 (95% CI: 0.9–3.6; $p = 0.084$).

Several studies have sought to assess the effect of asparaginase on outcomes in pediatric-inspired ALL regimens for adults. A retrospective, single-center study of 85 consecutive patients (aged 18–60 years) treated with the Dana-Farber Cancer Institute (DFCI) 91-01 protocol found that patients who received ≥80% of the planned asparaginase dose had higher 3-year OS ($p = 0.003$) and relapse-free survival (RFS; $p = 0.002$) and lower cumulative risk of relapse ($p = 0.01$) versus those receiving <80% of the planned dose due to tolerability issues [25]. However, because only 12 patients received <80% of the asparaginase dose, larger studies are necessary to confirm asparaginase dose as an independent prognostic indicator.

In a retrospective analysis of 95 adults with T-cell ALL/LBL at 3 large cancer centers between 2005 and 2015, asparaginase treatment as part of the initial regimen was associated with longer OS (HR: 2.3; $p = 0.02$) and RFS (HR: 2.7; $p = 0.01$) versus regimens without asparaginase [24]. After adjustment for age, sex, and WBC count, initial asparaginase use was still associated with improved RFS (HR: 3.2; $p = 0.03$) and better OS in patients aged <40 years (HR: 3.4, 95% CI: 1.2–9.5), but there seemed to be a trend toward decreased survival in patients aged >40 years (HR: 0.2, 95% CI: 0.03–1). A meta-analysis of 11 clinical trials found that higher doses of L-asparaginase were independently associated with improved outcomes for adults with T-cell acute lymphoblastic leukemia [43].

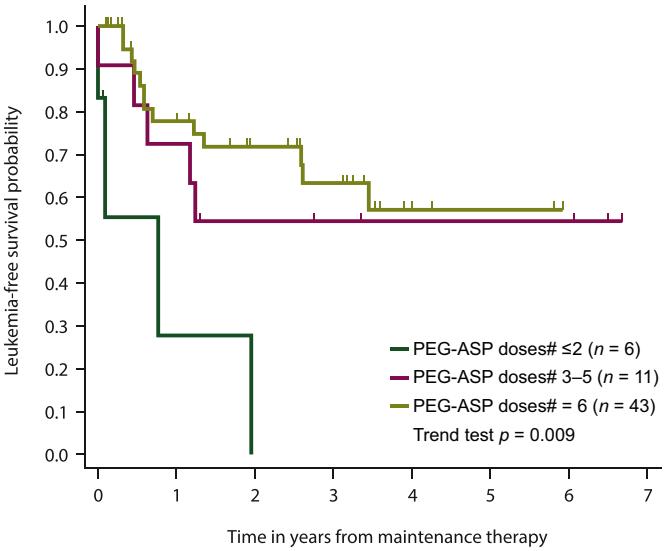

Fig. 1. A study in adults with ALL ($n = 60$; median age [range], 32 [18–59] years) treated with the BFM protocol, including a planned total of 6 pegaspargase (PEG-ASP) doses (2000 U/m^2 per dose), found that patients who received a higher number of PEG-ASP doses had significantly greater odds of leukemia-free survival versus those who received fewer doses (trend test $p = 0.009$). Reasons for not administering all planned doses included anaphylaxis, pancreatitis, treatment delay due to hyperbilirubinemia, and life-threatening thrombosis.

Figure permission: Republished with permission of the American Society of Hematology (ASH), from Aldoss I, et al. The number of peg-asparaginase doses administered is a determinant of relapse risk in adult ALL treated with a pediatric-like regimen. Blood 2013;122(21):3915; permission conveyed through Copyright Clearance Center, Inc. [44].

Table 2
PEG-ASP toxicity in adults with ALL treated with pediatric-inspired protocols in selected studies.

Study		Key PEG-ASP–related safety findings
Multicenter study in China [53]		• All patients had ≥1 AE; most were grade 1/2
n	30	• No treatment-related deaths or hypersensitivity reactions
Median age (range/SD), y	30 (18–62)	• 17% discontinued due to serious toxicity (1 with pancreatitis)
PEG-ASP dose	2500 IU/m^2	• 66.7% had grade 1/2 fibrinogen reduction
# PEG-ASP doses	6	• 50% had hypoalbuminemia
Single-center study in the United States [54]		• 50% of patients discontinued treatment early; causes included:
n	152	– Pancreatitis: $n = 15$
Median age (range/SD), y	35 (±12.4)	– Allergic reaction: $n = 7$
PEG-ASP dose	2000 IU/m^2	– Other, including HSCT, relapse, death: $n = 79$
# PEG-ASP doses	6	• Common PEG-ASP toxicities included:
		– Grade 3/4 transaminitis: 53.9%
		– Grade 3/4 hyperbilirubinemia: 23.7%
		– Grade 3/4 hypertriglyceridemia: 50.9%
		– Hypofibrinogenemia (<100 mg/dL): 47.9%
		– Grade 3/4 pancreatitis: 12.5%
		– Venous TE, any grade: 11.2%
		– Allergic reaction, any grade: 7.2%
		– Bleeding, any grade: 5.3%
UKALL14 [55]		• 17.8% of patients died during induction phase; half of deaths ($n = 8$; 8.9%) were accompanied by recognized PEG-ASP toxicities[b]
n	90	– Risk factors for induction death included age >40 y
Median age (range/SD), y	46.5 (25–65)[a]	• 51% of patients experienced ≥1 recognized grade 3–5 PEG-ASP toxicity, including:
PEG-ASP dose	1000 IU/m^2	– Grade 3–5 hepatotoxicity: 37.4% (hyperbilirubinemia: 24.2%)
# PEG-ASP doses	NR	– Grade 3–5 pancreatitis: 3.3%
		– Intracranial hemorrhage: 1.1%
		– Allergic reaction: 3.3%
		– Coagulation disorder: 4.4%
		– Vascular events: 6.7%
GMALL [38]		• PEG-ASP–associated grade 3/4 toxicities in cohorts 1/2 (see cohorts to left) included:
n	1226	– Increases in GOT or GPT: 30%/30%
Median age (range/SD), y	35 (15–55)	– Hyperbilirubinemia: 10%/16%
PEG-ASP dose	1000 IU/m^2: $n = 764$ (cohort 1)	– Thrombosis: 5%/5%
	2000 IU/m^2: $n = 382$ (cohort 2)	– Hypersensitivity: <1%/<1%
# PEG-ASP doses	NR	

Due to these results, the study protocol was amended to omit Day 4 PEG-ASP for patients aged >40 years, omit PEG-ASP entirely from induction treatment in patients with Ph+ ALL, and halve the daunorubicin dose to 30 mg/m^2 on Days 1, 8, 15, and 22 [55].
AE, adverse event; GGTP, gamma-glutamyl transpeptidase; GMALL, German Multicenter Study Group for Adult ALL; GOT, glutamate oxaloacetate transaminase; GPT, glutamate pyruvate transaminase; HSCT, hematopoietic stem cell transplantation; NR, not reported; PEG-ASP, pegaspargase; SD, standard deviation; TE, thromboembolism.
[a] 66% of patients were aged >40 years.
[b] The high death rate during induction of the UKALL14 trial was likely due to severe liver toxicity related to overlapping toxicity from treatment with PEG-ASP on Day 4, when patients were severely neutropenic (with sepsis), and treatment with myelosuppressive daunorubicin (60 mg/m^2).

Additionally, a retrospective review of 60 adult patients (aged 18–59 years) who were treated based on the COG 1882 pediatric protocol [32] (including 6 planned pegaspargase doses) found that a higher number of pegaspargase doses was associated with better leukemia-free survival versus a lower number of doses ($p = 0.009$ trend test; Fig. 1) [44]. It should be noted that many factors may correlate with the administration of a lower dose of asparaginase used, such as lower doses of other drugs used and a delay in treatment schedule. In particular, it is unknown whether reduced dosing of other therapies within a multi-agent treatment regimen confounds these findings. In the studies conducted by Storring et al. and Aldoss et al., the frequency and impact of reduced dosing of the other chemotherapeutic agents was not reported [25,44].

Other studies have compared adult ALL outcomes using asparaginase regimens and the dose-intensive hyperCVAD regimen (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), which is much more myelosuppressive but contains no or very little asparaginase. Retrospective analyses in adult patients with ALL have found better outcomes with asparaginase-containing regimens than with hyperCVAD [45,46]. However, other retrospective studies in AYA patients (aged 12–40 years) and adult patients (aged 21–73 years) with ALL reported similar outcomes between hyperCVAD and asparaginase-containing augmented Berlin-Frankfurt-Münster (BFM) regimens [36,47]. Furthermore, a decision-analytic model in AYA found that patients given a pediatric-inspired regimen including asparaginase had improved life-years and quality-adjusted life-years (QALYs) over 5 and 10 years (an increase of 0.25 and 0.32 life-years, respectively, and an increase of 0.18 and 0.24 QALYs, respectively) versus patients given hyperCVAD, although short-term, 1-year QALYs slightly favored hyperCVAD [48].

Little information regarding outcomes in adults treated with asparaginase therapy according to stem cell transplant (SCT) status has been published. In one study where adults aged 17 to 40 years received L-asparaginase during standard chemotherapy induction and intensification phases, 2-year EFS and 2-year OS for the whole cohort were 66% and 72% respectively; when censored for patients who underwent allogeneic SCT, these were 73% and 80%, respectively [34]. Similar findings were reported in a study of patients aged 15 to 60 years who received L-asparaginase as part of induction and consolidation therapy [49]. For the whole study cohort, 42-month EFS was 55% and 42-month OS was 60%; when censored for patients undergoing allogeneic SCT, these outcomes were also 55% and 60%, respectively. However, no comparisons were made with outcomes following allogeneic SCT in either study.

4. Toxicities of asparaginase in adults

Pegylated asparaginase is used as first-line in many countries, placing a major focus on this formulation; native EC-ASP is still available in the European Union and other countries but was withdrawn from the US market in 2012 [10]. Compared with EC-ASP,

Table 3
Asparaginase toxicities and their management [17,59].

Toxicity	Range of prevalence: grade 3/4, % patients	Management notes
Hyperbilirubinemia	24–39	Reversible; not an indication to permanently hold or adjust doses of subsequent asparaginase therapy; adjust other medications and hold asparaginase until grade 1 is achieved
↑Transaminases	36–54	Reversible; not an indication to permanently hold or adjust doses of asparaginase therapy; hold asparaginase until resolved to grade 2
Thrombosis	11–27	Start anticoagulation and maintain adequate platelet counts; asparaginase can be resumed while the patient remains on anticoagulation therapy for non–life-threatening thrombosis cases
Bleeding	<1	Rare
Pancreatitis	5–13	Permanent discontinuation of asparaginase due to high risk of recurrent pancreatitis if rechallenged; chemical pancreatitis is not an indication to hold subsequent doses of asparaginase
Hypersensitivity/allergic reaction	4–10	Replace with ***Erwinia*** asparaginase; administer corticosteroid and antihistamine
Hypofibrinogenemia (<100 mg/dL)	48–51	Replace with cryoprecipitate only during active bleeding or before procedures
Hyperglycemia	31–33	Reversible; not an indication to permanently hold asparaginase therapy; start insulin and other antiglycemic medications

pegylated asparaginase offers advantages of a longer half-life, less frequent dosing (3–4 weeks duration vs <3 days with EC-ASP), lower risk of hypersensitivity reaction/antibody development, and similar antileukemic activity [27,50,51]. A study in 25 adults with ALL found that a single intravenous (IV) dose (2000 IU/m^2) of pegaspargase on Day 16 of the BFM protocol was sufficient, as demonstrated by adequate levels of asparagine deamination and depletion, to replace the 14 EC-ASP doses typically used in the original protocol [52]. Given the utility and widespread use of pegaspargase, its specific AE and tolerability profile is of particular interest. Data on the safety and tolerability of pegaspargase from several studies in adult ALL are shown in Table 2 [38,53–55]. Collectively, these data suggest that risk factors for pegaspargase toxicities include increased age, obesity, and overlapping toxicities with myelosuppressive agents, such as daunorubicin, and with other comedications, such as anti-infectives and steroids [38,54–56].

In adults, few studies have compared the safety and/or efficacy of pegaspargase with EC-ASP in ALL [33]. One prospective, non-randomized study in 126 adults with ALL found no differences in CR, MRD levels following induction and consolidation, DFS, OS, or grade 3/4 toxicity during induction with pegaspargase versus EC-ASP, with the exception of a trend for higher hepatotoxicity with pegaspargase [33]. In a retrospective, single-center study of 122 adolescents and adults with ALL in China (aged 14–62 years) who were treated with EC-ASP or pegaspargase as part of an induction regimen [57], incidence of grade 3/4 hepatotoxicity, allergy, pancreatitis, and impaired renal function were similar with EC-ASP ($n = 76$) and pegaspargase ($n = 46$). However, patients treated with pegaspargase had a longer duration of agranulocytosis ($p < 0.001$) and a higher incidence of grade 4/5 infection ($p = 0.018$) versus those treated with EC-ASP. In the open-label, randomized DFCI 11-001 study in 237 children and AYA with ALL (aged 1–20 years), discontinuations were somewhat higher with calaspargase pegol-mknl than pegaspargase (33% vs 24%), but there were no substantial differences between groups for grade ≥3 AEs [58].

5. Enhancing asparaginase efficacy/tolerability in adults

Recommendations from an expert panel in 2011 for the prevention and management of toxicities associated with asparaginase stressed that efficient AE management may impact outcomes since asparaginase is a key component of ALL treatment, and discontinuations of treatment for toxicity could thus worsen outcomes [27]. Optimizing asparaginase safety is thus likely to improve ALL treatment efficacy. Key recommendations for management of asparaginase-related AEs in adults from 2018 and 2020 are summarized in Table 3 [17,59].

5.1. Hepatotoxicity

Considerable research on asparaginase safety and efficacy in adults has been published since the 2011 report [59]. High-grade hepatotoxicity has emerged as the most common AE associated with pegaspargase use in adults and appears to be dose- and age-related, occurring most frequently in older adults [29] and with higher doses and more intense dosing schedules; other risk factors include increased body mass index (BMI), low platelets, and low albumin (Table 4) [60]. Of note, high BMI is associated with more hepatic steatosis [61,62]. Among other studies of risk factors for asparaginase toxicity, a single-center study found that asparaginase-associated hepatotoxicity was increased in Hispanic patients versus Caucasian, African American, and Asian patients ($p = 0.02$), and there was a trend toward increased severity of hepatotoxicity and death with a BMI ≥25 [63]. Interestingly, hepatotoxicity also occurs at higher rates after the first pegaspargase dose [29,64]. The most common pegaspargase-associated toxicities to occur concomitantly with hepatotoxicity include infection/fever, hyperglycemia, and hyperbilirubinemia [64]. In a small retrospective case series of pediatric and young adult patients with asparaginase-related hyperbilirubinemia, L-carnitine was well tolerated and reduced bilirubin levels [65]. In a retrospective analysis of 25 patients with ALL who developed grade 3/4 hyperbilirubinemia after a single dose of pegaspargase, levocarnitine was no better than no intervention for reducing the time to hepatotoxicity resolution or the resumption of chemotherapy [66].

As the half-life of pegaspargase is approximately 5 to 7 days [52,67,68], timing of pegaspargase administration during induction chemotherapy has also been shown to impact outcomes with respect to hepatotoxicity. In the UKALL14 trial, dosing of pegaspargase on Days 4 and 18 (with daunorubicin on Days 1, 8, 15, and 21) was associated with deaths due to induction toxicity in 16 of 90 patients, largely among those aged >40 years; in 8 cases, sepsis and hepatotoxicity were both present [55]. The study protocol was subsequently amended so that patients aged >40 years received pegaspargase only on Day 18, and induction mortality was observed in only 2.5% of cases following this change [56]. Furthermore, in a study of 39 adults, when pegaspargase was given on Day 15 (with daunorubicin given on Days 1–3), although grade 3/4 hyperbilirubinemia was frequently observed, no deaths during induction therapy were reported [29]. Separately, a similar regimen resulted in neutropenic sepsis deaths in 3 of 51 patients following induction but none related to hepatotoxicity [32]. It is therefore suggested that during induction therapy, pegaspargase be administered 2 weeks after myelosuppressive drugs to reduce the likelihood of high-grade hyperbilirubinemia while patients are at increased risk of neutropenic sepsis [56].

5.2. Thrombosis

Reported incidence of asparaginase-related thromboembolism (TE) in adults with ALL has ranged from 3% to approximately 40% [25,31,53–55,69–72]. Asparaginase appears to reduce plasma levels of multiple coagulation factors, thereby affecting other components of

Table 4
Characteristics of patients with and without hepatotoxicity following treatment with PEG-ASP in a retrospective, university health system medical record cohort study[a] [60].

Characteristic	Univariate analysis			Multivariate analysis	
	No hepatotoxicity ($n = 84$)	Hepatoxicity ($n = 16$)	p value	OR (95% CI)	p value
Age, y, n (%)					
Median (range)	37 (18–76)	54 (18–79)	0.07		
Age ≥55 y	22 (26)	8 (50)	0.08		
Male sex, n (%)	46 (55)	10 (63)	0.60		
Body mass					
Median weight, kg (range)	79.1 (48.6–170)	96.4 (60–151)	0.01		0.007
Weight ≥90 kg, n (%)	12 (14)	6 (38)	0.04		
BSA, m^2 (range)	1.9 (1.46–2.9)	2.2 (1.63–2.79)	0.01		
BSA ≥2.0 m^2, n (%)	35 (42)	13 (81)	0.01	7.40 (1.73–31.61)	
CCI					
Median (range)	6 (0–19)	7 (6–11)	0.02		
CCI ≥7, n (%)	30 (36)	10 (63)	0.06		
Type 2 diabetes mellitus, n (%)	7 (8)	3 (19)	0.20		
CKD, n (%)	1 (1)	2 (13)	0.07		
CHF, n (%)	1 (1)	1 (6)	0.30		
Median WBC count, $10^3/m^3$ (range)	6.4 (0.4–376.6)	7.3 (0.7–48.4)	0.69		
Mean Hgb, mg/dL (SD)	9.9 ± 2.5	9.5 ± 2.0	0.56		
Platelets, $10^3/m^3$					
Median (range)	71 (5–647)	34 (4–332)	0.01		0.003
Platelets <50,000, n (%)	33 (39)	12 (75)	0.01	9.36 (2.12–41.17)	
Albumin					
Median (range)	3.4 (2.5–5)	3.2 (1.9–4.2)	0.41		0.038
Albumin ≤3.0 g/dL, n (%)	14 (17)	6 (40)	0.07	4.62 (1.09–19.68)	
Baseline liver function					
Median AST, U/L (range)	23 (9–155)	34 (18–144)	0.03		
Median ALT U/L (range)	35 (9–295)	48 (21–124)	0.05		
Median total bilirubin, mg/dL (range)	0.6 (0.1–1.9)	0.5 (0.3–1.2)	0.62		
Median direct bilirubin, mg/dL (range)	0.2 (0.1–1.2)	0.2 (0.1–0.6)	0.27		

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CCI, Charlson Comorbidity Index; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; Hgb, hemoglobin; OR, odds ratio; SD, standard deviation; WBC, white blood cell.
Table permission: Rausch CR, et al. PEGging down risk factors for peg-asparaginase hepatotoxicity in patients with acute lymphoblastic leukemia. Leuk Lymphoma 2018;59(3):617–24; reprinted by permission of the publisher (Taylor & Francis Ltd., http://www.tandfonline.com) [60].

hemostasis [72]. In a study of 25 adults aged 17 to 55 years with ALL treated with a regimen including only 1 dose of pegaspargase (2000 IU/m^2 IV), post-pegaspargase antithrombin III levels decreased below 50% of baseline in 67% of patients, which persisted for the duration of asparaginase activity [52]. A 2011 analysis of ALL clinical trials at DFCI found TE events occurred in 16 of 47 (34%) adult patients versus 27 of 501 (5%) pediatric patients; age was the only predictor of TE, with patients aged >30 years at very high risk (42%) [71]. The NOPHO study in 1772 patients with ALL found that the 2.5-year cumulative incidence of TE was 18.1% in patients aged 18.0 to 45.9 years, which was significantly higher than in children aged <10 years (3.7%; $p < 0.0001$) but not significantly greater than in patients aged 10 to 17 years (15.5%) [73]. Along with increased age, independent risk factors for TE in NOPHO included presence of a mediastinal mass and enlarged lymph nodes; additional risk factors for TE included use of a central venous line, immobilization, oral contraceptives, and genetic thrombophilic traits [73]. Studies have shown that TE may manifest as deep vein thrombosis, as pulmonary embolism, and also in association with central venous catheters, although the latter appears to be less frequent; approximately 8% to 23% of cases reported TEs [25,54,71,73]. In the NOPHO ALL2008 study, central venous catheters were present in 93% of cases of supradiaphragmatic TEs and 64% of symptomatic TEs [73].

Central nervous system (CNS) TE has been reported with asparaginase and has been associated with decreased OS and DFS [74]. Some clinical study data indicate that CNS TE comprises a higher proportion of thrombotic events in children than in adults, while adults experience a higher proportion of pulmonary embolism [72]. In the DFCI trial noted above, 2 CNS TE events occurred in adults, representing 11% of all thrombotic events, versus 7 events in children, representing 24% of all pediatric TEs [71]. This is consistent with NOPHO data showing that median age for patients with CNS TE was 11.1 years and for patients with pulmonary TE was 22.4 years [73]. The GRAALL study, which included 708 adults (aged 18–50 years) with ALL/LBL who received 8 EC-ASP IV doses (6000 IU/m^2), reported that CNS TE occurred in 22 (3.1%) patients, leading to death and persisting effects in 5% and 20% of cases, respectively [74]. No genetic risk factors for CNS TE were identified, and antithrombin prophylaxis with heparin appeared to be ineffective. In addition, a recent study in 186 Finnish adults with ALL found that neither asparaginase treatment nor increased BMI was associated with CNS TE in this population [75]. More than half (56%) of CNS TE cases in this study were diagnosed prior to asparaginase administration, which may have been partly confounded with the induction period, when CNS risk is highest and when asparaginase is usually initiated. These findings highlight the importance of other CNS risk factors, including advanced age, BMI, ALL disease subtype, and leukemia dissemination.

Standard management of TE is anticoagulation treatment (Table 3) [17]. The THROMBOTECT study in 949 children and adolescents (aged 1–18 years) with newly diagnosed ALL compared the prophylactic effects of low-dose unfractionated heparin, low-molecular-weight heparin (LMWH; enoxaparin), and activity-adapted antithrombin during the induction period [76]. TE occurred in 42 (4.4%) patients, and those randomized to unfractionated heparin (8.0%) had a higher incidence of TE versus those given enoxaparin (3.5%; $p = 0.011$) or antithrombin (1.9%; $p < 0.001$). Even in this pediatric population, increased age (particularly age >6 years) was associated with TE. Data from the DFCI trials show that 74% of patients received LMWH following TE and 19% received warfarin [71]. Asparaginase was restarted in 13 (81%) of the 16 adults with TE; while TE recurred in 7 (44%) adults, no TE-related deaths occurred. More recently, a Canadian single-center study assessed TE prophylaxis with weight-based enoxaparin in 41 adult patients aged 18 to 60 years being treated with intramuscular (IM) asparaginase under the intensification phase of the DFCI 91-01 regimen

[77]. TE rate was similar in the prophylaxis (18.9%) and nonprophylaxis groups (21.7%); TE occurred more frequently in patients receiving prophylaxis weighing ≥80 kg versus <80 kg (42.9% vs 4.4%; $p = 0.007$).

A follow-up DFCI study of anticoagulation TE prophylaxis reported similar results; 2-year cumulative incidence of TE was reduced to 28% for patients given prophylaxis versus 41% before prophylaxis was instituted [78]. The NOPHO study reported that 48 (17%) adults aged ≥17 years received LMWH and that 13% of these patients experienced first-time TE [73]. Only 3% of patients who received antithrombotic therapy had major bleeding complications, none of which were fatal, and 5% experienced a second TE event. Deaths directly attributable to TE occurred in 5 patients overall; risk of death was not significantly different in adults with and without TE. Another study in 75 adult patients with ALL receiving pegaspargase found that antithrombin supplementation had no significant effect on incidence of TE [79].

Fibrinogen cryoprecipitate replacement in adults with hypofibrinogenemia is known to increase the risk of TE [80]. Despite the high frequency of hypofibrinogenemia in adults with ALL receiving asparaginase therapy, this is typically not associated with an increased risk of major bleeding [54]. It has therefore been suggested that in patients with hypofibrinogenemia, cryoprecipitate replacement should be administered only during active bleeding or prior to procedures [59].

5.3. Pancreatitis

Adult ALL studies of pegaspargase have reported rates of pancreatitis ranging from approximately 3% to 24% [38,54,55,69]. Clinical pancreatitis, diagnosed when ≥2 of 3 criteria are fulfilled (abdominal pain, serum lipase or amylase ≥3 × upper limit of normal, and characteristic imaging findings of pancreatitis) [81], is an indication to permanently discontinue asparaginase based on high risk of recurrence; however, chemical pancreatitis does not indicate asparaginase discontinuation [17,27]. In a study of 5185 patients with ALL, 117 (2.3%) experienced acute pancreatitis. Independent clinical risk factors included high cumulative doses of asparaginase (≥240,000 U/m^2), older age, and Native American ancestry ($p < 0.001$ for all); the type of asparaginase formulation (pegaspargase or EC-ASP) did not affect pancreatitis rates [82].

Standard management of pancreatitis in adults with ALL remains generally unchanged from the 2011 expert panel recommendations [27] and includes early diagnosis and continuation of asparaginase with close monitoring in case of chemical pancreatitis and permanent discontinuation in case of clinical pancreatitis (Table 3) [17,59]. The 2011 guidelines also note that treatment with octreotide may be helpful [27], and more recent data suggest its efficacy [83,84], although the clinical practicality of octreotide prophylaxis is questionable.

5.4. Hypersensitivity and silent hypersensitivity

Development of clinical and silent hypersensitivity can be modulated by multiple factors, including asparaginase preparation, administration schedule, treatment protocols, and concomitant use of other chemotherapeutic agents [85]. For example, a study in 209 adults (aged 18–59 years) with B-cell ALL found that addition of rituximab significantly reduced the incidence of allergic reactions to EC-ASP (2% vs 11% in controls not given rituximab; $p = 0.002$) [86]. However, another study found that intensification with pegaspargase and rituximab in addition to other agents in 29 adults (aged 20–54 years) resulted in a 6.5% hypersensitivity rate [87].

Management of clinical and silent hypersensitivity while retaining asparaginase-based therapy is of keen interest, as a recent COG report showed that discontinuation of asparaginase due to toxicity was associated with inferior DFS in high-risk patients; however, high-risk patients who had their remaining doses of pegaspargase replaced by ER-ASP had outcomes similar to those who completed their scheduled asparaginase treatment [88]. Further, another COG study evaluated asparaginase activity in patients with National Cancer Institute high-risk ALL who received IV pegaspargase. Results showed that all patients who had plasma asparaginase level >0.02 IU/mL had undetectable plasma asparagine after 54 doses of pegaspargase administered during induction or consolidation [89]. These findings suggest that a lower dose of pegaspargase may be sufficient for some patients, which in turn, may reduce the likelihood of toxicities. In the GMALL study, although the majority of patients who received pegaspargase 500 IU/m^2 or 1000 IU/m^2 achieved serum asparaginase levels >0.1 IU/mL at 1 to 8 days after dosing, this was not maintained after 14 days in as many patients as was observed with 2000 IU/m^2 [90]. However, values for asparagine depletion were not reported.

ER-ASP has limited cross-reactivity with antibodies to EC-ASP/pegaspargase and can thus sustain therapeutic activity and asparaginase-associated improvements in clinical outcomes in patients who develop hypersensitivity [91,92]. Limited data available on ER-ASP use in adults with ALL demonstrate acceptable tolerability and efficacy in this age group. A 1998 study included 197 adults treated with EC-ASP and found that duration of leukemia-free survival was similar in patients who were switched to ER-ASP because of severe hypersensitivity reactions compared with patients who experienced either mild or no hypersensitivity reactions and received all planned EC-ASP doses [93]. A retrospective, single-center study evaluated hypersensitivity outcomes in 10 adults (aged 20–72 years) with ALL who were switched to ER-ASP following pegaspargase intolerance [94]; no hypersensitivity reactions or other asparaginase-related AEs occurred following the switch to ER-ASP, and no relapses in ER-ASP–treated patients were reported. In a subgroup analysis of a large compassionate use study of ER-ASP in patients with hypersensitivity reactions to EC-ASP, the safety profile of ER-ASP in the AYA population (aged ≥16–<40 years) was generally consistent with the overall population; incidence of hypersensitivity was lower in the AYA subgroup (10.9%) than in the youngest subgroup (≤10 years; 15.1%) [95].

6. Novel and emerging therapies and strategies for optimizing asparaginase treatment for adults

6.1. New asparaginase formulations

Novel formulations of asparaginase, including calaspargase pegol-mknl, recombinant ***Erwinia*** asparaginase, and asparaginase encapsulated in erythrocytes (eryaspase), may have potential for use in adult populations with ALL. Calaspargase pegol-mknl, an asparagine-specific enzyme, was approved by the US Food and Drug Administration (FDA) in December 2018 as a component of a multi-agent treatment of pediatric and AYA ALL [58]. Based on PK modeling, 99% of patients maintained serum asparaginase activity ≥0.1 U/mL during post-induction with calaspargase, and the safety profile was similar to pegaspargase [58]. Results from a phase 1 study of a recombinant ER-ASP (RYLAZE™, asparaginase *erwinia chrysanthemi* (recombinant)-rywn) in adult healthy volunteers showed complete asparagine depletion and no unanticipated AEs [96]. This recombinant ER-ASP is currently being evaluated in a phase 2/3 study (NCT04145531) and was approved in June 2021 for use in adult and pediatric patients with ALL who have developed hypersensitivity to ***E. coli***-derived asparaginase as a part of the Real-Time Oncology Review program [97]. The phase 2 NOR-GRASPALL 2016 study (NCT03267030) evaluated eryaspase in patients (aged 1–45 years) with ALL and hypersensitivity to pegaspargase (although only 2 adults were enrolled); eryaspase showed prolonged asparaginase enzyme activity and was well tolerated in the overall population [98].

6.2. Individualization of dosing

In recent years, studies using various true pediatric and pediatric-inspired protocols containing multiple post-remission asparaginase

doses at different levels and schedules and in varying adult age categories (although typically aged <55–60 years) have reported 5-year OS and EFS ranging from approximately 52% to 78% (Table 1) [11,28–36,38]. The use of varying age ranges reflects the debate over whether there is a maximum age for which pediatric-inspired regimens may be safe and effective [17]. Studies have commonly categorized adults by age groups, including [7,17,40]:

- AYA: age 15 to 39 years
- Adults: age 40 to <55 years
- Older adults: age 55 to 65 years

Over recent years, the uncertainty about potential tolerability of unmodified pediatric regimens or pediatric-based regimens in adults led to a broad variability of age groups defined for different treatment regimens. However, the National Comprehensive Cancer Network guidelines state that age alone is insufficient for determining patient fitness for therapy, and thus patients should be evaluated individually based on a broader range of factors [40].

Due in part to the complex and heterogeneous nature of asparaginase therapy, particularly across age ranges, monitoring serum asparaginase activity levels is key to ensure adequate asparagine depletion and to detect potential silent inactivation, which can lead to worse outcomes [85,99]. Although the optimal serum concentration for asparagine depletion has not been definitively determined, the therapeutically adequate threshold is ≥0.1 IU/mL [85,99]. The European Hematology Association discourages use of premedications, such as antihistamines and corticosteroids, to prevent hypersensitivity reactions because such measures may mask clinical allergy and thus expose the patient to the risk of insufficient asparaginase levels and worse outcomes [85]. However, a retrospective single-center study showed that premedication in combination with therapeutic drug monitoring demonstrated clinical benefit [100]. Furthermore, the adult CALGB 10403 protocol was amended to incorporate premedication and resulted in less allergic reaction [11].

Early and accurate identification of clinical reactions is key to successful management. Grade 1 or questionable reactions may present as overlapping symptoms of a non-allergic infusion reaction. Monitoring of serum asparaginase level within 3 to 7 days for pegaspargase and after the first dose and every reintroduction for EC-ASP to check for asparaginase activity and inactivation will confirm clinical allergic reaction and trigger switching to a non-***E. coli***–derived asparaginase. The presence of enzymatic activity will indicate a non-allergic reaction, and EC-ASP or pegaspargase can be continued. Grade 2 to 4 reactions indicate a switch from EC-ASP or pegaspargase to ER-ASP (6 doses at 25,000 IU/m^2 every other day to replace each dose of pegaspargase) or recombinant ER-ASP (when replacing a long-acting asparaginase product, the dosage of recombinant ER-ASP approved by the US FDA is 25 mg/m^2 administered IM every 48 h) [97]. Silent inactivation of pegaspargase is defined as a Day 7 serum level <0.1 IU/mL and/or a Day 14 level below the lower limit of quantitation. Patients who develop silent inactivation with EC-ASP (either the native form or pegaspargase) should be switched to a non-***E. coli***–derived asparaginase [85,99]. Study data suggest that prospective monitoring for silent inactivation, not only clinical reaction, and switching of asparaginase preparations in such cases may improve survival outcomes [88,101].

US researchers also proposed an algorithm specifically for monitoring pegaspargase activity and switching to ER-ASP (Fig. 2) [99], although it is difficult to estimate the use of serum asparaginase activity monitoring in clinical practice. In one study of 46 children and young adults, samples for serum asparaginase monitoring were collected following 17% of first pegaspargase doses, 73% of second doses, 53% of third doses, 66% of fourth doses, and 72% of fifth doses [102]. In one other pediatric study, universal serum asparaginase monitoring was completed in 87% of patients receiving ≥1 dose of pegaspargase, although this was assessed following implementation of a specific protocol, and monitoring persistence over time was not reported [100].

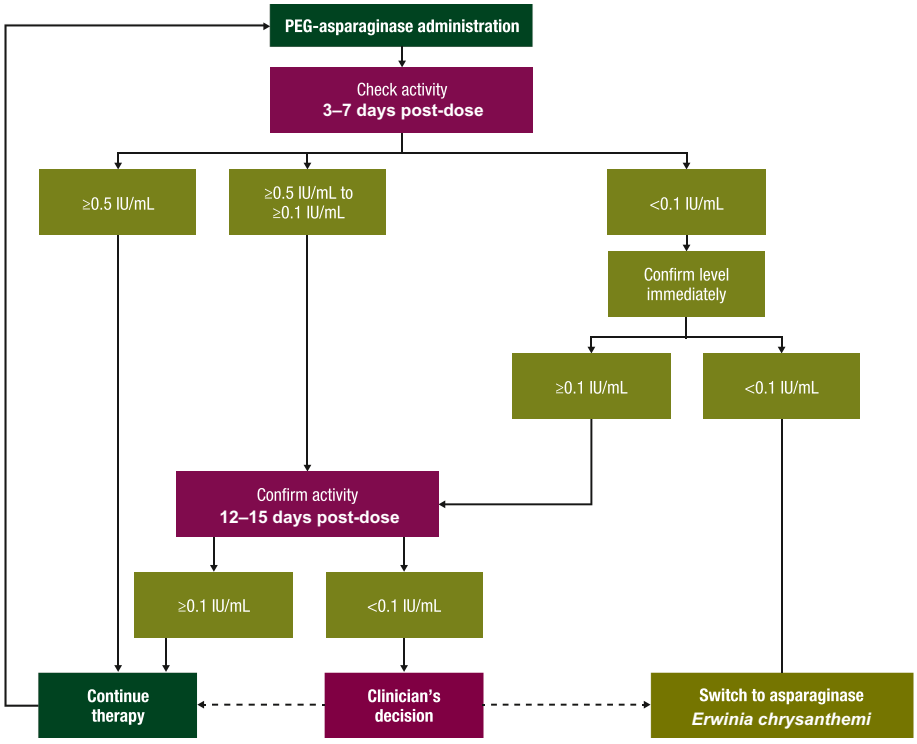

Fig. 2. Suggested algorithm for monitoring of pegaspargase activity as indicated by serum concentrations.
Figure permission: Salzer W, et al. Asparaginase activity levels and monitoring in patients with acute lymphoblastic leukemia. Leuk Lymphoma 2018;59(8):1797–806; reprinted by permission of the publisher (Taylor & Francis Ltd., http://www.tandfonline.com) [99].

6.2.1. Pharmacokinetic-based dosing

A strategy for optimizing the safety, tolerability, and benefits of asparaginase for adults with ALL is the use of PK-based dosing of pegaspargase [32]. In a US study in 51 adults aged 18 to 57 years with ALL [32], lower doses of pegaspargase (2000 IU/m^2 IV) and longer dose intervals of >4 weeks were utilized to reduce dose overlap and the resulting risk of toxicity because PK studies indicated stable asparagine depletion could be maintained, and timing of pegaspargase administration was synchronized with that of other chemotherapeutic drugs to avoid overlapping toxicities, which has been reported in other studies [55]. Drug-related toxicity led to discontinuation in 20% of patients. Seven-year DFS was 58% (74% in favorable-risk patients). In another study of 51 adult patients with ALL treated with a pediatric-inspired regimen, 26 received a reduced pegaspargase dose (≤1000; median, 500 IU/m^2/dose) and 25 received COG standard dosing (>1000; median, 2500 IU/m^2/dose). Estimated 2-year RFS was 63% in the reduced dosing group versus 73% in the standard dosing group ($p = 0.45$), and estimated 2-year OS for both groups was 74% ($p = 0.99$). The reduced dosing group experienced fewer grade 3/4 toxicities during induction ($p = 0.02$) while still achieving therapeutic asparaginase levels [103]. Notably, clinical trials in the European Union typically use lower doses of pegaspargase [28]. In this context, in patients who achieve very high levels of asparaginase activity, dose modifications (i.e., reductions) should be considered.

6.2.2. Pharmacogenetic profiling/risk assessment of patients

Several genetic traits and polymorphisms have been associated with response to asparaginase and other ALL therapies, suggesting such indicators may be useful in risk prediction and individualized treatment modulation. Among these, single nucleotide polymorphisms of the basic leucine zipper activating transcription factor 5 may be associated with decreased EFS [104]. The glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit 1 gene (***GRIA1***) and ***HLA-DRB1*0701*** were shown to be associated with hypersensitivity [104]. Genetic variants associated with asparaginase-related pancreatitis in children and young adults with ALL include a nonsense rare variant (rs199695765) in the ***CPA2*** gene (encoding carboxypeptidase A2) [82]. In addition, variants in the ***MYBBP1A***, ***SPEF2***, and ***IL16*** genes were associated with asparaginase-related AEs, including pancreatitis, hypersensitivity, and TE in children with ALL [105]. Lastly, another study discovered that the superoxide dismutase (***SOD2***) rs4880 CC genotype was associated with increased hepatotoxicity following asparaginase treatment and was more commonly found in the Hispanic population [106]. However, studies analyzing the correlations of genetic factors with response to ALL therapies and disease outcomes are lacking.

7. Special considerations for older adults

Treatment-related mortality rates in patients aged ≥55 years are approximately 20% to 40%, and estimated 5-year OS is approximately 10% to 20% [13]. Study data indicate that older adults (usually defined as aged ≥60 or ≥65 years) have higher incidence of multiple adverse prognostic factors [13,107]. Approximately half of older patients with ALL are Ph+, but bulky lymphadenopathy, elevated WBC counts, and mediastinal involvement are less common in older patients [13,107,108]. Common comorbidities in older adults with ALL include diabetes, cardiovascular disease, and other malignancies [107]. More generally, decrements in organ and physiological function adversely affect the pharmacology of ALL therapies in older patients [107]. Furthermore, asparaginase is poorly tolerated in older adults, particularly during the induction phase, where active leukemia contributes to the presence of a proinflammatory state [107,109]. For these reasons, lower asparaginase doses (100–500 IU/m^2) as well as new strategies based on more recently approved agents are prospectively being studied in patients aged >55 years.

Perhaps the most prominent risk of asparaginase in older patients is hepatotoxicity [59]. In the UKALLXII/ECOG2993 ALL trial of native asparaginase, CR and 5-year OS were worse in the 100 patients aged 55 to 65 years versus the 1814 remaining patients aged 14 to 54 years (73% vs 93% and 21% vs 41%, respectively; $p < 0.0001$ for both) [110]. Significantly more drug reductions, omissions, or delays occurred in the older subgroup ($p \leq 0.02$). Asparaginase was the most commonly omitted drug, accounting for almost a third of all cases, with hepatotoxicity as the most common reason.

Based on these risks, assessment of older adults should be based on clinical factors (comorbidities, organ function, performance status) and ability to receive intensive chemotherapy [13,108,111,112]. The selective use of asparaginase (e.g., dose reduction) and other modifications are prudent [113]. Encouraging trends include the promising results shown with combinations of chemotherapy with TKIs in Ph/BCR-ABL–positive ALL in older adults [19,20,108]. Moreover, asparaginase can be safely omitted from regimens prescribed for patients with Ph+ ALL. Positive safety and efficacy results have also been reported in adult patients treated with inotuzumab ozogamicin, a CD22 monoclonal antibody bound to calicheamicin [114,115], and with blinatumomab, an anti-CD19 bispecific antibody [116], which may herald a new era in adult ALL regimens.

8. Conclusions and future considerations

In summary, using asparaginase therapy in adult patients with ALL is a beneficial treatment strategy. Upcoming results of adult ALL trials should further clarify the role of asparaginase, particularly building on the results of the large NOPHO 2008, CALGB 10403, GRAALL-2005, GMALL 07/2003, and UKALL14 trials. Newer formulations of asparaginase, including calaspargase pegol-mknl, asparaginase erwinia chrysanthemi (recombinant)-rywn, and eryaspase, may have potential for use in adult populations with ALL. Further studies on the use of asparaginase-containing chemotherapy in combination with newer agents, such as blinatumomab or inotuzumab and TKIs, are being investigated. Finally, more studies are also needed on clinical, pharmacogenetic, and other predictors of response to asparaginase and how its risks can be modulated, including potential use of prophylactic approaches.

Practice points

- Using asparaginase regimens contributes to high survival rates in pediatric ALL; this may also be important for adults
- Studies using pediatric protocols in adults with ALL have reported 5-year OS and EFS rates of approximately 52% to 78%
- Common asparaginase-related toxicities in adults include hepatotoxicity, thrombosis, pancreatitis, and hypersensitivity
- More research is needed to evaluate the benefit/risk ratio of using asparaginase in adult ALL treatment regimens
- Upcoming results of adult ALL trials should further clarify the role of asparaginase in this patient population

Research agenda

- Investigation of optimal dosing and schedule of pegaspargase in asparaginase-based regimens for different subsets of adult ALL patients, such as older adults (aged >50–55 years), obese (high BMI) patients, and patients with specific comorbidities
- Further examination of the association between potential genetic risk markers and asparaginase-based regimen outcomes
- Further investigating approaches to manage specific pegaspargase-related adverse effects in adult patients, including dose reduction, the balance between drug discontinuation verses higher relapse rate, the value of therapeutic drug monitoring, and antithrombotic prophylaxis

Role of the funding source

Medical writing and editorial support for this work were provided by Jazz Pharmaceuticals.

Author contributions

Conceptualization: DD, NG, WS, NB. Data curation: DD, NG, WS, NB. Resources: DD, NG, WS, NB. Supervision: DD, NG, WS, NB. Validation: DD, NG, WS, NB. Writing - original draft: DD, NG, WS, NB. Writing - review & editing: DD, NG, WS, NB.

Conflict of interest statement

Dr. Douer has received fees for serving on advisory boards for and lecture and research funding from Pfizer, Amgen, Servier, Spectrum, Jazz, Gilead, and Bristol Myers Squibb. Dr. Gökbuget has served on an advisory board for Kite Pharma (uncompensated); has received fees for serving on advisory boards from Amgen, Pfizer, and Celgene/Juno Therapeutics; has received, travel support from Amgen and Pfizer; and has received grant support from Amgen. Dr. Stock has served on an advisory board for and received research funding from Sigma-Tau. Dr. Boissel has received honoraria from Amgen, Pfizer, Servier, Jazz Pharmaceuticals, and Novartis.

Acknowledgments

Medical writing and editorial assistance were provided by Larry Deblinger, of The Curry Rockefeller Group (CRG), and Nancy Tang, PharmD, of SciFluent Communications, Inc./Cello Health Communications, and were financially supported by Jazz Pharmaceuticals.

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