

Role of L-asparaginase in acute lymphoblastic leukemia: focus on adult patients

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Abstract: Asparaginase preparations deplete asparagine in acute lymphoblastic leukemia (ALL) blasts. Asparaginase in its various forms is an important component of treatment regimens for pediatric ALL. Recently, interest and use of asparaginase in adult patients with ALL has increased, particularly in young adults. There is much less information on asparaginase use and toxicity in adult compared with pediatric populations. This review surveys prior published studies of the three most commonly used asparagine preparations as used in adult patients, and discusses important toxicities encountered in adult patients who receive asparaginase preparations.

Keywords: asparaginase, leukemia, adults, children

Introduction

In 1953, Kidd noted the remarkable observation that guinea pig serum had antileukemia activity in mice.¹ The cause of this antileukemia activity was elucidated by Broome in 1961 and attributed to depletion of asparagines.² Quite rapidly, investigators confirmed the ability of *Escherichia coli* L-asparaginase to bring about remissions in children with acute lymphoblastic leukemia (ALL).³⁻⁶ L-asparaginase was initially envisioned as a targeted antileukemia drug, able to kill malignant lymphoblasts while not harming the normal cells of the patient, but this optimism proved to be short-lived; papers on anaphylactic shock and pancreatitis in conjunction with L-asparaginase rapidly appeared.^{7,8} Other toxicities of the drug have subsequently become well known.

L-asparaginase was incorporated into treatment protocols for children with ALL in the 1970s, and the drug has remained a consistent component of pediatric ALL treatment regimens. There are several excellent reviews and a multitude of published trials that detail the use of L-asparaginase and its derivatives, *Erwinia* asparaginase (*Erwinia*) and pegylated asparaginase, in pediatric patients.¹⁰⁻¹³ The use of L-asparaginase in adult patients with ALL is also prominent, although L-asparaginase is still not universally employed in standard adult ALL regimens, most notably the hyper CVAD (cyclophosphamide, vincristine, adriamycin, dexamethasone) regimen.^{14,15} Still, there is a surge of interest in the use of asparaginases, particularly PEG-asparaginase, in adults with ALL. *Erwinia* asparaginase is also generating interest, being principally substituted in patients with anaphylactic reactions to L-asparaginase or PEG-asparaginase.

This review describes the present use of asparaginase preparations in adults with ALL and the toxicities currently reported in this older group of patients. Similar to

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pediatric regimens, adult treatment protocols for ALL use initial induction treatment to induce remission quickly. Single-institution studies as well as multicenter studies from Europe and the United States all incorporate asparaginase into ALL regimens. However, not all adult ALL regimens include L-asparaginase, and intensive regimens not containing L-asparaginase can very successfully induce a complete response in adult patients.¹⁶ Along that line, Kantarjian et al reported successful induction using VAD (vincristine, adriamycin, dexamethasone) or cytoxan VAD in standard-risk adult ALL patients without using any asparaginase.¹⁵ Subsequent development of the hyper CVAD regimen at the MD Anderson Cancer Center did not incorporate L-asparaginase but did produce high complete response rates.^{14,15}

L-asparaginase

Asparaginase is currently used in three forms, ie, asparaginase manufactured from *E. coli*, asparaginase derived from *Erwinia chrysanthemi*, and L-asparaginase conjugated with polyethylene glycol (PEG). The chemistry and mechanism of action of asparaginase preparations has been detailed in multiple reviews.^{10,12,17,18} Briefly, cells require asparagine to proceed through the G1 cycle of cell division. Asparagine is important in protein, DNA, and RNA synthesis. Normal human tissues can synthesize asparagine via asparagine synthetase, but many malignant cells cannot do so. Thus, asparagine is an essential amino acid for tumor cells, but not for normal cells, and this can be exploited in designing treatment regimens for certain cancers. On the other hand, some malignant tumor cells demonstrate increased expression of asparagine synthetase, perhaps through endoplasmic reticulum stress pathways or amino acid response pathways. As expected, increased expression of asparagine synthetase corresponds to decreased sensitivity to asparaginase.

L-asparaginase from *E. coli*

L-asparaginase derived from *E. coli* has been used in acute leukemia therapy since the 1960s and is the most studied form of asparaginase. It has a fascinating history. The drug may be administered as an intravenous infusion or as an intramuscular injection. The drug has also been given to patients intrathecally.¹⁹ Initial studies of L-asparaginase in ALL evaluated the drug when it was given daily for as many as 28 consecutive days.²⁰ The half-life of the L-asparaginase enzyme and the enzymatic activity of asparaginase are similar, and do not appear to vary with repeated doses nor with the dose administered. The half-life of enzymatic activity is approximately 1.24 days in children.²¹ In adult patients

with leukemia, the drug is administered intravenously or intramuscularly, usually at doses of 25,000 U/m² given once or in regimens where 6000 U/m² are given every other day for six to nine doses. Depletion of serum asparagine is complete in the majority of children treated on a schedule of 2500–5000 IU/m² given every third day for eight doses. L-asparaginase does not cross the blood–brain barrier, but the drug does successfully deplete asparagine in the spinal fluid.^{22,23}

Erwinia asparaginase

The *Erwinia* asparaginase in use currently is produced by *E. chrysanthemi*. *Erwinia*, like asparaginase, may be administered intramuscularly or intravenously. *Erwinia* is currently approved for the treatment of leukemia in the United Kingdom. In the United States, an ongoing trial in children and adult patients with prior allergic reactions to other asparaginase preparations is finalizing information on the tolerability of *Erwinia* in order to obtain approval of the drug. The dose of *Erwinia* in this trial is 10,000 IU intramuscularly or intravenous every other day for six doses. The drug has previously been administered at similar doses and schedules as L-asparaginase, and several head-to-head comparisons with L-asparaginase have shown decreased efficacy for *Erwinia* as summarized by Pieters et al.²⁴ *Erwinia* has a decreased half-life compared with L-asparaginase, and the drug must be given at higher doses and more frequently than L-asparaginase in order to deplete asparagine completely.²¹ Asparagine levels also recover more quickly in patients receiving *Erwinia*, at least in children.²⁵ *Erwinia* has been demonstrated to be effective in patients with severe allergic reactions to L-asparaginase, and that is the most common clinical setting in which clinicians use *Erwinia*.²⁶ Another application of *Erwinia* might be in patients with silent antibody formation to *E. coli* asparaginase preparations. These patients rapidly clear asparaginase unbeknownst to their physicians. *Erwinia* asparaginase may circumvent this rapid clearance and allow for better asparagine depletion.²⁶ Currently, testing for silent antibodies is not routinely done on most protocols.

PEG-asparaginase

Pegylation of *E. coli*-derived asparaginase increases the circulation time for the asparaginase enzyme and decreases the immunogenicity of asparaginase. PEG-asparaginase pharmacokinetics are otherwise similar to those of native asparaginase.¹² The drug shows one-compartment distribution, a monophasic half-life, and a single elimination phase. The prolonged half-life is the most important characteristic of the drug.

PEG-asparaginase has a half-life of about 6 days, considerably longer than the *E. coli* or Erwinia preparations. A single dose of PEG-asparaginase may be substituted for a series of injections of nonpegylated asparaginase. Antibodies formed against asparaginase or PEG alter the clearance of the drug. Patients who have had overt allergic reactions to L-asparaginase have a shorter half-life for PEG-asparaginase than patients without prior reactions to asparaginase preparations.¹⁰ In addition to overt allergy, a shortened half-life may be encountered in the setting of occult antibody formation.²⁶ Patients with silent antibodies might benefit from a switch to Erwinia asparaginase or a more frequent dosing of PEG-asparaginase.²⁶ Patients with antibodies to PEG also clear the drug more rapidly than patients without antibodies to PEG, as demonstrated by Armstrong et al.²⁷ Interestingly, development of PEG antibodies could be on the increase in the general population, because PEG is used in a variety of commonly encountered products, including cosmetics and processed foods. Routine testing for antibodies to PEG is not done, but might be worthwhile in newly diagnosed adult patients who are to receive regimens that contain PEG-asparaginase.

***E. coli* asparaginase in adult trials**

Adult ALL protocols routinely incorporate asparaginase as part of therapy. As in pediatric trials, the intensity and schedule of asparaginase treatment vary markedly. As opposed to pediatrics, not all successful adult ALL therapies use asparaginase in treating ALL. Notably, the hyper CVAD regimen used at MD Anderson Cancer Center initially did not employ asparaginase and has excellent induction results and event-free survival in young adults with ALL. Still, most trials performed on adult ALL patients from the early 1970s demonstrated that a moderate fraction of patients could be cured using complex regimens that employed asparaginase. Results from several large trials are shown in Table 1. L-asparaginase was typically given every other day for several doses, biweekly, or the drug was given on consecutive days for up to 2 weeks.³¹ The dose in most protocols ranged from 5000 to 10,000 IU/m², given on multiple days.

Table 1 Doses of *Escherichia coli* asparaginase in adult trials

Reference	n	Asparaginase dose	Overall survival
Schauer et al ²⁸	72	L-asparaginase 200 IU/kg	50%
Lister et al ²⁹	51	L-asparaginase	20%
Marcus et al ³⁰	69	L-asparaginase 10,000 IU/m ²	32%
Hoelzer et al ³⁴	162	L-asparaginase 5000 IU/m ²	44%

In the 1980s, results from large adult ALL trials that employed asparaginase were reported and showed minimal improvement in event-free survival. Doses continued to vary from one protocol to another. A randomization between 4 or 12 doses of L-asparaginase 10,000 IU/m² during induction failed to show any improvement or worsening in disease-free survival in a large Medical Research Council trial.³² L-asparaginase was generally used early in therapy, in induction or consolidation, or both. Protocols were disparate on the timing of asparaginase, with several studies starting L-asparaginase on the first day to the fifth day of induction, while other protocols did not introduce L-asparaginase until approximately day 100 of therapy or later. The dose of L-asparaginase varied widely between protocols in the 1980s. Commonly used doses were in the range of 6000–12,000 IU/m² given on consecutive or alternate days.^{16,33,34} A few protocols dosed L-asparaginase based on weight, with a dose range of 200–500 IU/kg.³⁵ Such weight-based dosing might prove toxic given the current epidemic of obesity. Interestingly, one protocol was able to administer 60,000 IU of L-asparaginase intravenously three times weekly for 2 weeks.³⁶ Still, when compared with pediatric protocols, adult studies in the 1980s tended to introduce asparaginase later in induction, and exposure to L-asparaginase was considerably briefer than what is typically seen in pediatric trials. In GMALL 04/89, Ludwig et al used L-asparaginase 10,000 IU/m² following intravenous methotrexate during weeks 13, 15, and 17 for a total of three doses, with a significant improvement in clinical complete response compared with their prior regimen.³⁷

In the 1990s, studies in adult patients continued apace. L-asparaginase dosing was much more uniform in reported studies, with 6000–10,000 IU/m² being generally used. However, the frequency and timing of L-asparaginase administration remained far from uniform. Ribera et al reported perhaps the most intensive use of L-asparaginase, with 16 doses of 10,000 IU/m² in induction and consolidation followed by 20,000 IU/m² given twice in delayed intensification.³⁸ The very large international trial in adults with ALL conducted by the Medical Research Council/Eastern Cooperative Oncology Group used L-asparaginase at the relatively conventional dose of 10,000 IU/m² initially, then changed to 10,000 IU as a flat dose on days 17–28 of induction.³⁹ Three more doses of L-asparaginase 10,000 IU were given in the first 3–4 weeks following induction with no further asparaginase delivered in this international trial. The timing of L-asparaginase therapy in the different published regimens remained variable. While use in induction and consolidation was the norm, the timing

of asparaginase therapy in induction ranged from early in the first week of therapy to as late as the ninth week of treatment. Again in the 1990s, the hyper CVAD regimen with no use of asparaginase achieved an excellent remission rate and a long-term overall survival rate comparable with those regimens for adults that contained L-asparaginase. Similarly, a large Japanese study randomized adults to therapy with or without L-asparaginase and found no significant difference in outcome between the two groups.⁴⁰

Since 2000, L-asparaginase has been slowly replaced by the pegylated form of asparaginase, mostly due to the notable convenience of dosing. Still, there have been significant trials that incorporated L-asparaginase and reported in the last decade, particularly in younger adults. The Dutch-Belgian Hemato-Oncology Cooperative Group evaluated a pediatric-based regimen for patients aged 17–40 years.⁴¹ This protocol used 21 scheduled doses of L-asparaginase at the conventional dose of 6000 IU/m². Nine doses of L-asparaginase were administered starting immediately after a prednisone prephase, and further doses occurred later in therapy, similar to the design of pediatric therapy. In a much larger trial, Huguet et al administered an intensive ALL treatment regimen to patients aged 15–60 years. L-asparaginase was introduced on day 8 of induction, 2 weeks after a prednisone window.⁴² The dose of L-asparaginase was 6000 IU/m² for six doses in induction, with doses of 10,000 IU/m² given approximately every 3 weeks in consolidation for six doses. A repeat course of 6000 IU/m² given every other day for six doses was given in delayed intensification. In the above study, patients over 45 years of age had an unacceptable toxic death rate. The Spanish group used L-asparaginase successfully in a trial for young adults up to 30 years of age with ALL.⁴³ L-asparaginase was started on day 10 of therapy. Fifteen doses of L-asparaginase 10,000 IU/m² were given during induction and consolidation, and one dose of 20,000 IU/m² was given in the reinduction phase. Outcomes were similar between adolescent patients and adults on this regimen up to the age of 30 years. Much less L-asparaginase was used by Labar et al in their randomized trial.⁴⁴ L-asparaginase was not given in induction, but rather approximately three doses of 10,000 IU/m² were given starting at day 66 of therapy.

***Erwinia* asparaginase in adult trials**

Erwinia asparaginase has been used in the past in at least two forms, ie, *E. chrysanthemi* and *E. carotavora*. Currently, *E. chrysanthemi* is used. An extensive search of the literature showed no evaluations of *Erwinia* asparaginase as frontline therapy for adult ALL patients. However, the

drug has been studied extensively as second-line or later therapy, and there are multiple ongoing studies that employ *Erwinia* asparaginase in second-line or third-line treatment of ALL in pediatrics. The use of *Erwinia* asparaginase in adults with ALL parallels pediatric use, with the drug being substituted as a second-line or third-line form of asparaginase. In pediatric trials, the drug is routinely given at 10,000–20,000 IU/m² two or three times per week. The drug is a regular substitution for adult and pediatric patients who are allergic to L-asparaginase or PEG-asparaginase preparations. In adult trials, *Erwinia* asparaginase is most often given every other day, reflecting the short half-life of the drug, with the most frequent dose being 10,000 IU/m².^{21,24} A current clinical trial of *Erwinia* asparaginase is enrolling both children and adults who have had allergic reactions to PEG-asparaginase. This trial may lead to approval of *Erwinia* asparaginase in the United States. At the present time, there is no significant evidence that demonstrates superior clinical efficacy for intramuscular versus intravenous *Erwinia*, nor is there any conclusive evidence that one route is more likely to cause toxicity than another.

PEG-asparaginase in adult trials

Due to its prolonged half-life and prolonged depletion of asparagine, PEG-asparaginase has proven to be attractive as an alternative to the other asparaginase forms. In addition, pegylation of asparaginase may lead to fewer allergic reactions. PEG-asparaginase has been studied in adult patients since at least the early 1980s. In 1981, Park et al evaluated the pharmacology of a PEG adduct of asparaginase in four adult patients.⁴⁵ This initial pharmacology study was followed by a larger Phase I/II trial that studied the pharmacology of PEG-asparaginase in 37 adult patients at the MD Anderson Cancer Center.⁴⁶ Doses of 250–8000 IU/m² were evaluated. An open-label Phase II trial of PEG-asparaginase was performed in 1995.⁴⁷ This trial used 2000 IU/m² given every 2 weeks as a single agent in 18 adults with ALL. PEG-asparaginase 2000–2500 IU/m² given intravenously or intramuscularly is the standard adult dose. Some current studies impose a cap at 3750 IU per dose. Given the prolonged half-life of the drug, a 2–3-week interval between doses may be effective. A handful of studies have evaluated PEG-asparaginase in combination chemotherapy regimens for adults with newly diagnosed or relapsed ALL. The CALGB (Cancer and Leukemia Group B) study 9511 incorporated PEG-asparaginase 2500 IU/m², with a cap at 3750 IU, for four doses.⁴⁸

Aguayo et al used PEG-asparaginase at 2500 IU/m² (maximum dose 3750 IU) in a combination regimen for relapsed ALL.⁴⁹ The Berlin–Frankfurt–Munster group used PEG-asparaginase in protocol 05/93 and allowed intrapatient dose escalation according to asparaginase levels. A 500–1000 IU/m² dose escalation was assessed, and the escalation was well tolerated.⁵⁰

Many adult protocols are attempting to recapitulate pediatric-based therapy for de novo ALL in an attempt to improve treatment results in younger adult patients. As pediatric trials have moved to PEG-asparaginase, so too has PEG-asparaginase use in the young adult population become prominent. Douer et al has successfully used a dose of 2000 IU/m² of PEG-asparaginase on day 16 of induction for adults up to age 55 years with newly diagnosed ALL.⁵¹ At the University of Texas MD Anderson Cancer Center, adults up to the age of 40 years are given 2500 IU/m², with a total of seven doses administered during the first 6 months of treatment; the PEG-asparaginase dose is not capped.⁵² The CALGB has started a multi-institution evaluation of pediatric-based therapy in young adults with ALL that also uses PEG-asparaginase 2500 IU/m² administered throughout treatment, as is done in pediatric-based ALL treatment regimens.

Asparaginase toxicities in adult trials

Pancreatitis

All three asparaginase preparations have been implicated in causing pancreatitis. In children, a randomized trial of PEG-asparaginase versus L-asparaginase for standard risk ALL showed no significant difference in the incidence of grade 3–4 pancreatitis.⁵³ In children, the incidence of pancreatitis with asparaginase may increase with patient age, which implies that adults should have higher rates of pancreatitis than children.⁵⁴ This has not been confirmed in several studies of adults treated with pediatric-based regimens. In the studies by Huguet et al and Ribera et al, no clinically significant cases of pancreatitis were reported.^{42,43} Similarly, no pancreatitis was seen in 26 adult patients studied with escalating doses (500–1000 IU/m²) of PEG-asparaginase,⁵⁰ nor is pancreatitis noted to be a toxicity in several other adult trials.^{41,47,55} However, in general, the incidence of pancreatitis in conjunction with asparaginase is generally assumed to be about 5%–10%.^{13,53} Generally, if a combination of clinical plus radiographic or biochemical findings confirm pancreatitis is present, further use of asparaginase is not recommended.

Thrombosis and hemorrhage

Thrombus formation is a significant worry when using asparaginase in adult patients. The incidence of thrombotic complications in patients on asparaginase-containing regimens varies from less than 10% to greater than 30%.⁵⁶ The incidence of thrombus formation increases with the age of the patient population. In adults, central lines are frequently placed in the arm rather than into a subclavian vein. The smaller caliber vein may contribute to thrombus formation. Pooled data on PEG-asparaginase, published in abstract form, indicates thrombus formation occurs in approximately 5%–15% of adult patients when PEG-asparaginase is used.⁵² Further information is needed concerning PEG-asparaginase and thrombosis, especially in older adults; more extensive information in children so far has shown that PEG-asparaginase is not associated with increased thrombosis.^{57–60} The timing of thrombus formation is generally early in therapy; the GOELAMS study found a 9.3% incidence during induction,⁶¹ possibly related to confounding factors, such as hypercoagulability due to the active leukemia and placement of new central lines. The type of induction corticosteroid also influences thrombus formation during asparaginase therapy, with prednisone being associated with a higher risk of thrombosis.^{62,63} The incidence of thrombotic events appears to be about equivalent when comparing *Erwinia* asparaginase and L-asparaginase. After the diagnosis of an asparaginase-induced thrombus, low molecular weight heparin has been used with success, and asparaginase therapy may be restarted in patients who have had adequately treated thrombotic events.⁵⁶ The value of antithrombin III infusions is not clear, though the GOELAMS investigators did show a decrease in thrombosis when prophylactic antithrombin III infusion was used.⁶¹

Serious hemorrhagic complications secondary to depleted clotting factors are less frequent than thrombotic events during asparaginase therapy.⁶¹ Fibrinogen levels frequently fall during therapy, but the issue of fibrinogen replacement at an agreed upon fibrinogen level has not been settled; a fibrinogen level less than 1 g/L frequently triggers replacement therapy.

Liver toxicity

As noted in prior reviews, there are limited specific data on liver toxicity and asparaginase use. Most ALL regimens employ several potentially hepatotoxic drugs, such as high dose corticosteroids, vinca alkaloids, anthracyclines and antimetabolites. In addition, adult leukemia patients often receive antifungal prophylaxis with azoles, and adults have

other causes of hepatic toxicity, including alcohol. Quantifying the hepatic toxicity of asparaginase in such patients is difficult. Early evaluations of L-asparaginase at doses as high as 1000 IU/kg caused hepatic dysfunction in up to 75% of patients.⁶⁴ Lower doses of asparaginase, including PEG-asparaginase, result in less hepatic toxicity, but liver toxicity is still prominent.^{47,51,52,56} In the great majority of adult patients, these abnormalities resolve over time.

Immunological reactions to asparaginase

Hypersensitivity reactions to asparaginase preparations are not rare and can be serious. The risk of a severe allergic reaction changes depending on prior exposures and concomitant medications (corticosteroids). In induction regimens that use high-dose steroids, allergic reactions to asparaginase are infrequent. In 1500 adults treated on the Medical Research Council UKALL XII/Eastern Cooperative Oncology Group E2993, a 90% induction success was reported for a well-tolerated induction regimen that employed high-dose prednisone and multiple injections of L-asparaginase.³⁹ There was no mention of allergic reactions to asparaginase. Similarly, multiple authors have noted no severe allergic reactions to PEG-asparaginase in adults during asparaginase therapy.^{41,50,52,65,66} It seems likely that with repeated exposures and while patients are not receiving corticosteroids, allergic reactions become more prominent and probably occur in approximately 5%–10% of patients.^{67,68} An allergic reaction rate of 10% or greater is more in keeping with the larger pediatric experience with asparaginase. A purported advantage of PEG-asparaginase is that it is less immunogenic than L-asparaginase. Still, severe allergic reactions clearly occur in patients who get repeated doses of PEG-asparaginase.^{51,52} Patients who have allergic reactions to L-asparaginase or PEG-asparaginase may be successfully treated with *Erwinia* asparaginase. In the main, antibodies to PEG-asparaginase and L-asparaginase do not cross-react with *Erwinia*. Allergic reactions to *Erwinia* can occur in up to one third of children.⁶⁸ Much less is known about the incidence of severe allergic reactions in adults treated with *Erwinia* after prior severe allergic reactions to the other asparaginases.

Summary

Asparaginase is a prominent component of therapy in many modern adult ALL treatment protocols, though there are a few exceptions. Recent interest in adapting pediatric regimens for use in young adults has increased asparaginase exposure, especially in this group of patients. Native

L-asparaginase, and now PEG-asparaginase, are regularly employed in frontline treatment of ALL in young adults. As with pediatric patients, severe allergic reactions, thrombosis, pancreatitis, and hepatic injury are prominent with asparaginase use. The incidence of these toxicities increases with age. *Erwinia* asparaginase is commonly substituted in cases of allergy to L-asparaginase or PEG-asparaginase. In cases of thrombus formation, patients may be successfully retreated with asparaginase once the initial thrombus has been treated. Prophylaxis for thrombus formation may prove to be helpful, but more data are needed. Pancreatitis remains a difficult obstacle to further asparaginase treatment. Given that it precludes most subsequent uses of asparaginase, the diagnosis of pancreatitis must be confirmed by both symptoms and clinical studies. For PEG-asparaginase, an optimal dose and schedule has not been clearly established. An inpatient dose-escalation trial of PEG-asparaginase might help to guide PEG-asparaginase dosing in adults with ALL.

Disclosure

The author has served on an advisory board for Sigma Tau Pharmaceuticals.

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