

Hypersensitivity reactions to L-asparaginase do not impact on the remission duration of adults with acute lymphoblastic leukemia

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Among its multiple toxic effects, L-asparaginase induces allergic reactions that may reduce its biological effect. The impact of hypersensitivity reactions on the duration of leukemia-free survival (LFS) was assessed in adults with newly diagnosed acute lymphoblastic leukemia (ALL) receiving intensive multi-agent chemotherapy. In CALGB study 8811 (*Blood* 1995; 85: 2025–2037), 197 adults were scheduled to receive 14 doses of *Escherichia coli* L-asparaginase (6000 U/m² SC) during 7 of the first 12 weeks of chemotherapy. No further L-asparaginase was given. Chemotherapy was given for 24 months. The median follow-up time has been 5.7 years. Of the 141 patients who remained on study after 12 weeks, 82 (58%) had received all 14 planned doses; 38 (27%) had 12–13 L-asparaginase doses documented in their treatment record; 21 (15%) patients had received ≤ 11 doses due to a variety of toxic effects. The mean number of doses received prior to experiencing any hypersensitivity reaction was seven (range 1–11). Seven patients had mild hypersensitivity reactions, but all seven eventually received 12–14 doses of *E. coli* L-asparaginase. Twenty-one other patients had severe hypersensitivity reactions that required discontinuation of *E. coli* L-asparaginase; 20 of these patients were switched to Erwinia L-asparaginase to complete their treatment. Ultimately, 12 of these 20 patients received 14 doses of L-asparaginase in total, and six received 12–13 doses. Thus, only three of the 21 patients who had severe hypersensitivity reactions received ≤ 11 total L-asparaginase doses. Other L-asparaginase-related complications included pancreatitis (15 patients), hypofibrinogenemia <100 mg/dl (29 patients), and deep venous thrombosis or pulmonary embolism (eight patients); some of these patients had L-asparaginase discontinued after these complications. The estimates for LFS at 3 years were 55% (95% confidence interval, 44–65%) for the patients who received all 14 L-asparaginase doses (median LFS, 5.1 years), 47% (95% CI, 33–62%) for those who received 12–13 doses, and 48% (95% CI, 29–67%) for those who received ≤ 11 doses. There were no significant differences between these three groups in the length of LFS ($P = 0.68$). LFS did not correlate with a history of severe hypersensitivity reaction ($P = 0.67$). In general, *E. coli* L-asparaginase was well tolerated in these adult patients, and most patients received all of the planned therapy. Patients who had mild L-asparaginase hypersensitivity reactions and patients who switched to Erwinia L-asparaginase because of more severe allergic reactions did not have significantly shorter LFS than the remaining adults treated on this ALL protocol. The possibility that *E. coli* L-asparaginase is inactivated or destroyed in those individuals who have become hypersensitive to it becomes less important when allergic patients are secondarily treated with Erwinia L-asparaginase.

Keywords: L-asparaginase; acute lymphoblastic leukemia; chemotherapy; hypersensitivity

Introduction

Since the antitumor effects of L-asparaginase were first recognized more than 30 years ago,¹ it has become an important

drug in the treatment of childhood acute lymphoblastic leukemia (ALL). It has been proven effective both as a single agent and as part of multidrug combination regimens.^{2–7}

Although it causes minimal myelosuppression, L-asparaginase can produce significant toxicity due in part to inhibition of normal protein synthesis (Table 1). Well-recognized toxic effects include hepatic dysfunction, pancreatitis, coagulopathy, hyperglycemia, and central nervous system (CNS) abnormalities, in addition to nausea, vomiting, fatigue and anorexia. L-asparaginase also causes hypersensitivity reactions which are life-threatening in some patients.^{8–10} Most often, these follow repeated exposures, but anaphylaxis may occur after the first injection. The incidence of hypersensitivity reactions depends on the route and schedule of administration, and on other drugs given concomitantly.¹¹ Since intramuscular (i.m.) or subcutaneous (s.c.) administration is as effective as intravenous (i.v.) administration and has fewer toxic effects and less severe allergic reactions, it has become the method of choice.¹² Even so, i.m. administration has been associated with a 6–32% incidence of allergic reaction in children.^{5,12}

Until recently, *Escherichia coli*-derived L-asparaginase has

Table 1 Toxic effects of L-asparaginase

Allergic reactions
Anaphylaxis
Fever, chills
Cutaneous reactions (erythema, urticaria, wheal and flare, hives, induration)
Protein synthesis inhibition
Hyperglycemia (hypoinsulinemia)
Hypoalbuminemia (edema)
Low fibrinogen (<100 mg/dl)
Prolonged partial thromboplastin time (PTT)
Prolonged prothrombin time (PT)
Decreased protein C
Coagulopathy
Deep venous thrombosis (inferior vena cava, cavernous sinus)
Pulmonary embolism
Bleeding
Pancreatitis
Nausea, vomiting, epigastric pain
Pseudocyst
Liver dysfunction
Elevated bilirubin
Elevated transaminase levels
Fatty metamorphosis
Neurotoxicity
Confusion, somnolence, coma
Renal
Azotemia
Acute renal failure

been the only commercially available form in the USA. Erwinia carotovora-derived L-asparaginase, which is available in Canada, England, and Europe, has been used in the USA only in patients with an allergy to *E. coli* L-asparaginase. Previous studies have found that the antigenically distinct form of Erwinia L-asparaginase has comparable efficacy and no cross reactivity with *E. coli* L-asparaginase. Thus, it is an acceptable substitute for patients who are allergic to the *E. coli* protein.^{13–15}

Recently, the Cancer and Leukemia Group B (CALGB) tested a new intensive chemotherapy regimen for adults with untreated ALL.¹⁶ This phase II trial (Study 8811) produced a high rate of complete remissions (85%) and a high proportion of durable remissions in patients from 16 to 80 years old with a median leukemia-free survival (LFS) of 29 months. It used a five-drug induction regimen including cyclophosphamide, daunorubicin, vincristine, prednisone, and *E. coli* L-asparaginase. One novel aspect of this trial was the more extensive use of L-asparaginase than has previously been used in adult ALL treatment protocols, namely, biweekly subcutaneous administration for 7 weeks during the first 12 weeks of therapy.

Although most reports of toxicity and hypersensitivity reactions to L-asparaginase have been confined to children, the perception exists that this agent is poorly tolerated by adults. In this retrospective examination of the CALGB 8811 trial, we have focused on hypersensitivity reactions and toxicity to L-asparaginase in adult patients. Hypersensitivity reactions included localized swelling, erythema, urticaria or anaphylaxis, while pancreatitis, hypofibrinogenemia, hyperbilirubinemia, deep vein thromboses, pulmonary emboli, and encephalopathy were the observed toxicities. The data were also analyzed to determine whether patients who had toxic reactions requiring discontinuation of L-asparaginase treatment had a shorter remission duration than did patients who received all 14 planned doses. Our hypothesis was that patients whose treatment was truncated, or those who manifested immune-mediated hypersensitivity reactions to L-asparaginase thus neutralizing its biological activity, could have experienced less anti-leukemic effect, and this would be reflected by shorter durations of remission.

Materials and methods

The data for these analyses were compiled from a retrospective review of the charts from the CALGB 8811 clinical trial. The details of this clinical trial have been previously published.¹⁶ Patients were eligible for the CALGB 8811 trial if they had untreated ALL or acute undifferentiated leukemia.¹⁷ The diagnosis of ALL was confirmed by central review of blood smears and bone marrow specimens for cytological and cytochemical features according to the French–American–British (FAB) criteria.^{18,19} Immunophenotyping and cytogenetic analyses were performed to confirm the diagnosis.

L-asparaginase was only administered during the induction and early intensification phases of treatment. The drug was given twice per week for six doses during remission induction (course I) and again for four doses each during course IIA (weeks 7 and 8) and course IIB (weeks 10 and 11). Each L-asparaginase dose was given s.c., usually in the buttocks but occasionally in the thigh or upper arm. The complete chemotherapy dosages and schedule for the first 12 weeks of treatment are listed in Table 2. Total treatment, including central nervous system prophylaxis and maintenance chemotherapy, lasted for 24 months.¹⁶

Between September 1988 and June 1991, 214 patients were enrolled on the CALGB 8811 trial. One withdrew and 16 were ineligible due to the wrong diagnosis (either acute myeloid leukemia or lymphocytic lymphoma). Of the remaining 197 patients from the study, 56 were not further evaluated in this retrospective analysis either because of lack of complete clinical information (four patients) and/or because the patient did not complete the first 12 weeks of chemotherapy. Seventeen of these 56 died during induction and 13 had disease that was refractory to treatment. Twenty-six achieved a complete remission (CR) but were taken off this protocol at that point for alternative therapies; 12 of these patients later died or relapsed within the initial 12 week period, 10 died or relapsed beyond the first 12 weeks, and four were still in CR at last follow-up. Thus, for this study, we analyzed only the 141 ALL patients with complete data who completed the first 12 weeks of planned treatment on the protocol. In this way we defined a group of relatively uniformly treated patients with ALL in whom the effects of L-asparaginase hypersensitivity reactions on remission duration could be isolated and examined.

For this analysis, we counted the number of doses of L-asparaginase that were documented on the flow sheets as having been given to each patient. The prescribed number of treatments per protocol was 14; however, in many cases, 14 doses were not received. In four cases, one to three extra doses were recorded, possibly as errors in documentation. In 59 cases, fewer than 14 doses were recorded. According to the protocol, L-asparaginase was to be withheld due to moderate or severe side-effects or if the patient were too ill to receive any more chemotherapy at that particular time. In addition, fewer than 14 doses may have been recorded due to poor documentation or to missing doses (physician error). We decided a priori that we would group together patients who received ≥ 14 doses, 12–13 doses, and ≤ 11 doses. In a number of cases, an improper dosage was recorded; however, each individual exposure was counted as a dose even if considerably less than the correct dose were given. This was done because the primary event being investigated in this study was one of hypersensitivity, and frequency of exposure was deemed more important than total dose.

The occurrence and severity of possible hypersensitivity reactions were determined from notes recorded in the chart documenting concurrent observations. A 'mild' reaction was generally erythema, induration, and swelling at the injection site (grade 1 or 2 by the NCI Common Toxicity Criteria). A 'severe' reaction to L-asparaginase (grade 3 or 4 toxicity) was distinguished by whether the treating physician deemed it necessary to change from *E. coli* L-asparaginase to Erwinia L-asparaginase or to discontinue further L-asparaginase treatment altogether. There is some ambiguity in this area since some patients with a 'mild reaction' by clinical description were changed to Erwinia L-asparaginase, and thus, were categorized as a 'severe reaction' for the purpose of this analysis. Physicians tended to react on the side of safety, and therefore some cases of mild hypersensitivity have been called 'severe reactions' using these definitions. In other cases, patients with mild local reactions continued to receive *E. coli* L-asparaginase, sometimes following pretreatment with an antihistamine (usually diphenhydramine).

Other side-effects attributable to L-asparaginase were also noted. Pancreatitis was recorded if there were clinical symptoms and if elevated levels of amylase or lipase were measured. Also assessed were hypofibrinogenemia (<100 mg/dl), elevation in total bilirubin (>1.4 mg/dl), the presence of any deep vein thrombosis or pulmonary embolus, and encephalo-

Table 2 Remission induction and intensive consolidation chemotherapy

Course I: remission induction (4 weeks)			
Cyclophosphamide ^a	i.v.	1200 mg/m ²	day 1
Daunorubicin ^a	i.v.	45 mg/m ²	days 1, 2, 3
Vincristine	i.v.	2 mg	days 1,8,15,22
Prednisone ^a	p.o./i.v.	60 mg/m ² /d	days 1–21
L-asparaginase	s.c.	6000 IU/m ²	days 5,8,11,15,18,22
^a For patients >60 years old:			
Cyclophosphamide	i.v.	800 mg/m ²	day 1
Daunorubicin	i.v.	30 mg/m ²	days 1,2,3
Prednisone	p.o./i.v.	60 mg/m ² /d	days 1–7
Course IIA: early intensification (4 weeks)			
Intrathecal methotrexate		15 mg	day 1
Cyclophosphamide	i.v.	1000 mg/m ²	day 1
6-Mercaptopurine	p.o.	60 mg/m ² /d	days 1–14
Cytarabine	s.c.	75 mg/m ² /d	days 1–4, 8–11
Vincristine	i.v.	2 mg	days 15,22
L-asparaginase	s.c.	6000 IU/m ²	days 15,18,22,25
Course IIB: repeat course IIA once (4 weeks)			

lopathy. The protocol required that the serum fibrinogen level be measured prior to each L-asparaginase dose and that transfusions of fresh frozen plasma or cryoprecipitate be given to maintain a concentration >100 mg/dl.

The relationship between the occurrence of major side-effects or hypersensitivity reactions and the duration of LFS was analyzed with the univariate Cox regression model.²⁰ The number of L-asparaginase (*E. coli* and/or Erwinia) doses received was analyzed similarly. LFS and remission duration were defined to be the interval from date of CR to relapse or death. LFS curves were drawn using Kaplan–Meier probability estimates.²¹ Data were current as of April 1997, and patients still alive without relapse were censored for the statistical analysis at their date of last contact.

Results

The 141 patients in this study consisted of 65% males and had a median age of 29 years (range 16–74 years). At diagnosis, they had a median hemoglobin of 9.4 gm/dl (range 4.0–16.6), median platelet count of 56 500/ μ l (range 8000–557 000), and a median leukocyte count of 13 400/ μ l (range 700–475 000). By immunophenotyping and cytogenetic analyses, it was known that 35 patients had a T cell or TMy+ immunophenotype, 11 patients were known to have the Philadelphia chromosome, and 44 others were known to have a B lineage or BMy+ immunophenotype.

Of the 141 fully evaluable patients, only 82 (58%) received all 14 assigned doses of L-asparaginase. Thirty-eight patients (27%) had 12–13 doses recorded. Although many of those might have received all 14 doses, it was not documented in their treatment record. Twenty-one patients (15%) had 11 or fewer doses recorded. Six patients received only three to six doses each; that is, these patients received L-asparaginase only during the first course of remission induction therapy and not subsequently. Eight patients received seven to 10 doses of L-asparaginase (ie during courses I and IIA but not subsequently).

Toxicity

Twenty-eight patients (20%) had documented hypersensitivity reactions to *E. coli* L-asparaginase (Table 3). Of these 28 reac-

Table 3 Number of toxic events observed in 141 adults with ALL receiving L-asparaginase

	No. of doses of L-asparaginase received			
	≥14	12–13	≤11	Totals
No. of patients	82	38	21	141
Severe hypersensitivity reaction	12	6	3	21
Changed to Erwinia L-asparaginase	12	6	2	20
Mild hypersensitivity reaction	4	3	0	7
Pancreatitis	0	4	11	15
Fibrinogen <100 mg/dl	17	9	3	29
Total bilirubin >1.4 mg/dl	21	9	8	38
DVT or PE	2	3	3	8

DVT, deep vein thrombosis; PE, pulmonary embolism.

tions, 20 (14% of all patients) were considered severe enough to switch to Erwinia L-asparaginase, whereas eight patients (6%) continued to receive *E. coli* L-asparaginase. Ultimately, 12 of these 20 patients received 14 doses of L-asparaginase in total, and six received 12–13 doses. Thus, only three of the 21 patients who had severe hypersensitivity reactions received ≤11 total L-asparaginase doses. The mean number of doses received prior to any hypersensitivity reaction was seven with a range of 1–11. In only one case was a reaction to Erwinia L-asparaginase noted (following the third dose); however, the patient still managed to receive all four additional doses with the aid of antihistamine pretreatment.

Fifteen patients (11%) were found to have clinical and biochemical evidence for acute pancreatitis. Eleven of these patients received ≤11 doses because further L-asparaginase treatment was discontinued after the occurrence of pancreatitis. Twenty-nine patients (21%) were found to have at least one fibrinogen level below 100 mg/dl. Seven patients (5%) had deep vein thromboses, and one patient had a pulmonary embolus. There was only one reported case of encephalopathy due to L-asparaginase; however, that patient was not included within this analysis since he died before the end of course II.

Table 4 Univariate Cox regression results of the relationship between L-asparaginase treatment and side-effects with the leukemia-free survival of 141 patients with ALL

Variable	Coefficient ^a	Logrank χ^2	P value
Number of doses ^b	-0.05	0.92	0.34
Severe reaction	0.13	0.18	0.67
Mild or severe reaction	-0.004	<0.01	0.99
Pancreatitis	0.65	4.13	0.04
Hypofibrinogenemia	-0.10	0.11	0.74
Hyperbilirubinemia	0.19	0.56	0.46
DVT or PE	-0.08	0.02	0.88

^aA positive coefficient indicates that the presence of the side-effect is related to a shorter LFS while a negative coefficient indicates the converse.

^bThe total number of doses of L-asparaginase (*E. coli* and/or *Erwinia*) was analyzed as a continuous variable. The negative sign indicates that a fewer number of doses is associated with shorter LFS, although this was not statistically significant.

Impact on leukemia-free survival

Seventy-five of the 141 patients (53%) have had a relapse of ALL. There was no significant relationship between the total number of doses of L-asparaginase received and the duration of LFS, based on the Cox model ($P = 0.34$; Table 4). After a median follow-up time of 5.7 years, the estimates for LFS at 3 years were 55% (95% confidence interval, 44–65%) for patients who received all 14 doses (median LFS, 5.1 years), 47% (95% CI, 33–62%) for those who received 12–13 doses, and 48% (95% CI, 29–67%) for those who received ≤ 11 doses. Figure 1 shows a Kaplan–Meier plot of the LFS for these groups. There were no significant differences overall in the length of LFS ($P = 0.68$, based on two degrees of freedom logrank test).

The six patients who received L-asparaginase only during the remission induction course I (≤ 6 doses total) had a median LFS of 0.6 years. The eight patients who received L-asparaginase only during courses I and IIA (7–10 doses total) had a median LFS of 1.2 years. The estimates for LFS at 3 years were 33% (95% CI, 12–65%) for the former group of six patients and 38% (95% CI, 16–66%) for the latter group of eight patients. The 127 patients who received some L-aspar-

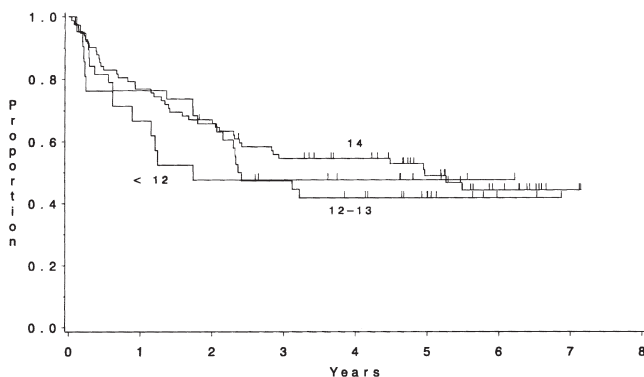


Figure 1 The leukemia-free survival is shown for 141 adults with ALL after a median follow-up time of 5.7 years. The estimates of LFS at 3 years were not significantly different ($P = 0.68$): 55% (95% CI, 44–65%) for the 82 patients who received 14 doses of L-asparaginase (median 5.1 years), 47% (95% CI, 33–62%) for the 38 patients who received 12–13 doses (median 2.4 years), and 48% (95% CI, 29–67%) for the 21 patients who received <12 doses (median 1.5 years).

aginase during all three treatment courses I, IIA and IIB (11–14 doses total) have had a median LFS of 4.7 years. Their estimated LFS at 3 years was 54% (95% CI, 45–62%). The first two groups are quite small for making comparisons. If they are combined and patients who received ≤ 10 doses (during courses I and IIA only) are compared with those who received 11–14 doses during all 3 monthly blocks of treatment, then the median durations of LFS are 1.2 years and 4.7 years, respectively. This difference is not statistically significant by the logrank test ($P = 0.17$).

The occurrence of major side-effects or hypersensitivity reactions was approximately equivalent between subsets of patients characterized by a T/TMy or B/BMy immunophenotype or with the Philadelphia chromosome (data not shown). The relationships between major side-effects or hypersensitivity reactions and LFS are presented in Table 4. The 15 patients who developed pancreatitis had a median LFS of 1.2 years, while patients who did not develop this side-effect had a median LFS of 5.0 years ($P = 0.04$). The estimates for LFS at 3 years were 33% (95% CI, 16–56%) for those who had pancreatitis and 54% (95% CI, 45–62%) for those who did not. Figure 2 shows a Kaplan–Meier plot of the LFS for these two groups.

Discussion

The primary objective of this study was to ascertain whether adult ALL patients who experienced hypersensitivity reactions to *E. coli* L-asparaginase had shorter durations of complete remission. Presumably these patients would likely have had less exposure, either due to discontinuation of this treatment or by immune complex inhibition of the enzyme effect. Twenty percent of the adults who remained on study after the first 3 months of treatment had had some form of hypersensitivity reaction to L-asparaginase. This is consistent with the percentage of children who have hypersensitivity reactions to *E. coli* L-asparaginase (6–32%).^{5,12} Because the L-asparaginase was given early in the treatment program when our patients were profoundly immunosuppressed both by their disease and by this corticosteroid-containing chemotherapy regimen, the incidence of hypersensitivity reactions may have been less than if the same exposure had been given later in the treatment course.

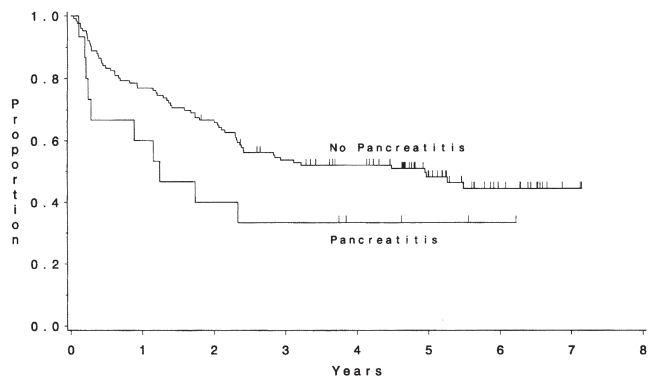


Figure 2 The leukemia-free survival is shown for 15 patients who developed pancreatitis (median 1.2 years) and for 126 patients who did not develop pancreatitis (5.0 years). The difference was statistically significant ($P = 0.04$) by logrank test. The estimates of LFS at 3 years were 33% (95% CI, 16–56%) for those who had pancreatitis and 54% (95% CI, 45–62%) for those who did not.

This study found no statistically significant differences in LFS based on the total number of doses of L-asparaginase (*E. coli* and/or Erwinia) given to a patient, regardless of hypersensitivity ($P = 0.34$). Three categories were also used for comparison (≥ 14 doses, 12–13 doses, or ≤ 11 doses). It is possible that the first several weeks of L-asparaginase treatment in the CALGB 8811 trial made the more extensive use over the full 12-week period unnecessary. However, we cannot conclude that the first three to six doses provided as much benefit as the full course of 14 planned doses. In fact, there appears to be some long-term benefit for those patients who received L-asparaginase during all three treatment courses. A prospective, randomized trial would be required to assess the true contribution of any specific duration of L-asparaginase therapy to the overall outcome.

It was also important to determine whether there was a correlation between LFS and hypersensitivity reactions. Patients who had any documented hypersensitivity reaction, mild or severe, did not have shorter durations of remission ($P = 0.99$). There was also no significant effect on LFS when analyzing only the severe hypersensitivity reactions ($P = 0.67$). The interpretation of these results is difficult because, on average, patients who had hypersensitivity reactions received the same total number of doses of L-asparaginase (13.3) as did those patients who did not have hypersensitivity reactions (12.7). The possibility that *E. coli* L-asparaginase is inactivated or destroyed in those individuals who have become hypersensitive to it becomes less important when allergic patients are secondarily treated with Erwinia L-asparaginase since Erwinia L-asparaginase appears equally effective as *E. coli* L-asparaginase and bears no cross-reactivity. Because serum asparagine levels were not measured in this study, it is unknown whether prior doses had been complexed and inactivated within the allergic patients. In most cases, patients were quickly changed to Erwinia L-asparaginase. Thus, it is likely that these patients did not have a significantly diminished total L-asparaginase therapeutic effect.^{14,15}

Pharmacokinetic studies of different L-asparaginase preparations demonstrate that the half-life for the enzyme activity in serum is dependent on the particular enzyme preparation used.²² The half-life for *E. coli* L-asparaginase is approximately 1.4 days and for Erwinia L-asparaginase is approximately 0.65 days. The newer pegylated formulation, PEG-asparaginase, has a considerably longer half-life, approximately 5.7 days. However, patients who have experienced a hypersensitivity reaction to *E. coli* L-asparaginase have a decreased apparent half-life if retreated with either the native *E. coli* enzyme (undetectable) or the PEG-modified L-asparaginase (approximately 1.8 days).

The patients selected for this detailed analysis would be expected to have a better outcome than an unselected newly diagnosed ALL patient. We included only those who finished three courses of therapy on protocol so that the impact of L-asparaginase treatment on long-term outcome could be determined. This design eliminated patients who died early or were taken off protocol for other treatment. Thus, the patients analyzed within this study were the ones who were better able to tolerate this rigorous treatment protocol, and the ability of these people to receive this intensive chemotherapy may obscure any marginal benefit to be gained from more extensive L-asparaginase treatment.

Billett and co-workers¹³ found that 22.6% of children with ALL who had hypersensitivity reactions to *E. coli* L-asparaginase also had reactions to Erwinia L-asparaginase. They concluded, however, that this was not due to cross-reactivity.

They found no predictive factors for an allergic response to either form of L-asparaginase, and they concluded that Erwinia L-asparaginase is a good alternative to *E. coli* L-asparaginase.¹³ Our findings are similar since only one out of the 20 (5%) adult patients who were hypersensitive to *E. coli* L-asparaginase showed a subsequent reaction to Erwinia L-asparaginase. This patient had only a mild reaction after his third dose and was able to receive all four of his remaining doses of Erwinia L-asparaginase after pretreatment with antihistamines.

Finally, the only positive correlation found was between patients with pancreatitis and a shortened LFS ($P = 0.04$). A number of factors may have contributed to this relationship. Eleven of 15 patients diagnosed with pancreatitis received 11 or fewer doses of L-asparaginase. The average number of doses received was eight. These particular patients had no known predisposing factors for pancreatitis, but other causes of pancreatitis are possible and were not specifically excluded. In particular, all patients received large doses of glucocorticosteroids. Although the lesser exposure to L-asparaginase given to these patients may be related to their worse outcome, these patients often received no chemotherapy or reduced doses of all of their chemotherapy drugs while acutely ill with pancreatitis. All cases of pancreatitis developed in patients receiving *E. coli* L-asparaginase and none had received Erwinia L-asparaginase. It has been reported that Erwinia L-asparaginase less frequently causes pancreatitis because the enzyme is more confined to the intravascular space than the *E. coli* enzyme and thus less likely to infiltrate into the pancreatic tissues.²³

In general, *E. coli* L-asparaginase was well tolerated in these adult patients, and most patients received all of the planned therapy. Patients who had mild L-asparaginase hypersensitivity reactions and patients who switched to Erwinia L-asparaginase because of more severe allergic reactions did not have significantly shorter LFS than the remaining adults treated on this ALL protocol. The possibility that *E. coli* L-asparaginase is inactivated or destroyed in those individuals who have become hypersensitive to it becomes less important when allergic patients are secondarily treated with Erwinia L-asparaginase.

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