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***Erwinia* Asparaginase after Allergy to *E coli* Asparaginase in Children with Acute Lymphoblastic Leukemia**

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Abstract

Background—*E coli* asparaginase is an important component of treatment for childhood acute lymphoblastic leukemia (ALL); however, hypersensitivity develops in up to 30% of patients. We assessed the nadir enzyme activity and tolerability of *Erwinia* asparaginase, an alternative preparation, in *E coli* asparaginase-allergic patients.

Patients and Methods—Between 2000-2002, 215 children with newly diagnosed ALL were enrolled on Dana-Farber Cancer Institute ALL Consortium Protocol 00-01 and were to receive 30 weekly doses of intramuscular *E coli* asparaginase. If *E coli* asparaginase allergy developed, patients were switched to twice-weekly intramuscular *Erwinia* asparaginase (25,000 IU/m²). Nadir serum asparaginase activity (NSAA) was measured every 3 weeks.

Results—Forty-two patients (20%) developed *E coli* asparaginase allergy and switched to *Erwinia*. Of 38 patients with evaluable samples, 34 (89%) *Erwinia*-treated patients had at least one

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therapeutic NSAA (< 0.1 IU/mL). The median NSAA was 0.247 IU/mL 3 days and 0.077 IU/mL 4 days after an *Erwinia* dose. Associated toxicities included allergy in 14 (33%) and pancreatitis in 3 patients (7%). At a median follow-up of 5.4 years, event-free survival ($\pm$ standard error) of the 42 patients who switched to *Erwinia* was $86 \pm 5\%$ compared with $81 \pm 3\%$ for the 170 patients without *E coli* asparaginase allergy ($p = 0.55$).

Conclusions—Twice-weekly *Erwinia* asparaginase was well-tolerated and achieved a therapeutically effective NSAA in most *E coli*-asparaginase allergic patients. Development of *E coli* allergy and subsequent treatment with twice-weekly *Erwinia* did not adversely impact event-free survival. *Erwinia* asparaginase should be considered for *E coli* asparaginase-allergic patients.

Keywords

leukemia; childhood; asparaginase; *Erwinia*

Introduction

Asparaginase has been a universal component of therapy for childhood acute lymphoblastic leukemia (ALL) since the 1970's. Most of the commonly used asparaginase preparations are derived from the bacteria *Escherichia coli* (*E coli*). However, up to 30% of patients develop an allergic reaction to native *E coli* asparaginase which limits its use.[1-3] Allergic symptoms range from mild, local erythema at the site of intramuscular (IM) injection to severe anaphylaxis.[2,4-6]

Erwinia asparaginase, derived from the *Erwinia chrysanthemi* bacteria, is an alternative preparation that is antigenically distinct from and has a considerably shorter biological half-life than *E coli* asparaginase.[7-9] *Erwinia* asparaginase has been administered to patients who have experienced allergy to native and polyethylene glycosylated (PEG) *E coli* asparaginase.[5,10-12] However, there are few published reports regarding the pharmacokinetics, tolerability, and long-term outcomes of children who received *Erwinia* asparaginase after *E coli* asparaginase allergy. Additionally, the optimal dosing schedule of *Erwinia* asparaginase after previous *E coli* asparaginase allergy remains unclear. We report here the experience of 42 patients treated between 2000 and 2002 on Dana-Farber Cancer Institute (DFCI) ALL Consortium Protocol 00-01 who received twice weekly *Erwinia* asparaginase following an allergic reaction to *E coli* asparaginase.

Patients and Methods

Patients

Between September 2000 and December 2002, 215 children (age 1 to 18 years) with newly diagnosed ALL were enrolled on DFCI-ALL Protocol 00-01 and began an intensification phase which included 30 consecutive weeks of asparaginase beginning on week 7 of therapy. Only patients who were alive and in complete remission at the start of the intensification phase (and so had the opportunity to develop *E coli* asparaginase allergy) were included in this analysis. Patients were enrolled at the following participating institutions: DFCI/Children's Hospital Boston (Boston, MA); Maine Children's Cancer Program (Scarborough, ME); University of Rochester Medical Center (Rochester, NY); Columbia University Medical Center (New York, NY); Ochsner Clinic, New Orleans; McMaster University Medical Center (Hamilton, Ontario); San Jorge Children's Hospital (San Juan, PR); Hospital Sainte Justine (Montreal, Quebec); Le Centre Hospitalier de L'Universite, Laval (Quebec City, Quebec). The institutional review board at each participating institution approved the protocol prior to patient enrollment. Written informed consent was obtained from parents or guardians prior to initiating therapy.

Therapy

Details of treatment on DFCI-ALL Consortium Protocols have been previously published. [1,13] Differences between Protocol 00-01 and previously published DFCIALL Consortium protocols included: (1) a randomized comparison of fixed dosing of *E coli* asparaginase (based upon body surface area) and individualized dosing (based upon determinations of nadir serum asparaginase activity (NSAA) every 3 weeks), [14] and (2) a randomized comparison of two corticosteroids, dexamethasone and prednisone, during all post-induction phases of treatment. [15]

Patients were classified as standard risk (SR) if they met all of the following criteria: age 1-9.99 years, white blood cell count <50,000/ μ L, B-precursor phenotype, diagnostic spinal fluid with fewer than 5 leukocytes per high power field (CNS1 or CNS2 status), and absence of a mediastinal mass. All others were designated as high risk (HR). Patients with Philadelphia chromosome positive (Ph+) ALL were treated as HR but underwent allogeneic hematopoietic stem cell transplantation in first remission. Patients with MLL-rearranged ALL received additional intensification chemotherapy after remission, followed by HR treatment. [16] Patients with persistent leukemia at the end of the one-month induction phase were removed from the protocol. [17]

All patients were scheduled to receive 30 weeks of intramuscular (IM) *E coli* asparaginase beginning 7 weeks after diagnosis. In the event of an allergic reaction to *E coli* asparaginase, *Erwinia* asparaginase was substituted at a dose of 25,000 IU/m² administered IM twice weekly at 3-day and 4-day intervals. Patients who experienced a subsequent allergic event while receiving *Erwinia* asparaginase were then switched to weekly IM PEG-asparaginase at a dose of 2,500 IU/m². Asparaginase treatment was withheld in the setting of mild/moderate pancreatitis or deep venous thrombosis, and resumed when symptoms resolved. Asparaginase was permanently discontinued in the event of severe pancreatitis or allergic reaction to all preparations of asparaginase.

In January 2003, *Erwinia* asparaginase became unavailable. Ten patients who were receiving *Erwinia* asparaginase at that time were switched to weekly IM PEG-asparaginase for the remainder of their planned asparaginase treatment. These patients received a median of 8 weeks of *Erwinia* asparaginase prior to the switch to PEG asparaginase (range, 4 to 20 weeks). Toxicity and serum asparaginase activity data are included for these patients only for the time that they were receiving *Erwinia* asparaginase.

Asparaginase-Related Toxicities

Data regarding hypersensitivity, pancreatitis, hyperglycemia (requiring insulin), thrombosis, and bleeding were prospectively collected. Hypersensitivity reactions were classified as mild (local reaction only at IM injection site, including erythema and/or swelling) or severe (defined as all other allergic reactions, including rash or urticaria beyond the injection site, lip/tongue swelling, respiratory distress, or hypotension). As noted above, the asparaginase preparation was switched upon the occurrence either a mild or severe hypersensitivity reaction.

Pancreatitis was defined as abdominal or back pain accompanied by a rise in pancreatic enzymes (serum amylase and/or lipase). Pancreatitis was considered to be severe if symptoms persisted for more than three days. All other cases of pancreatitis were considered mild/moderate. All cases of thrombosis were confirmed by radiographic imaging.

Determination of Asparaginase Activity

NSAA was monitored in samples obtained every three weeks from patients just prior to the administration of the next dose of asparaginase. Blood (2.5 mL) was collected and allowed to clot for 30 minutes before centrifuging for 10 minutes at 1,300 *g*. Serum was stored at -70°C until packaged for shipment to the analytical laboratory in a sufficient quantity of dry-ice to ensure that the samples remained frozen during transit. Asparaginase activity was determined by a coupled enzymatic assay as previously reported with minor modifications. [9] Briefly, aspartic acid formed from the asparaginase catalyzed deamination of asparagine reacts with α -ketoglutaric acid in the presence of glutamic-oxaloacetic transaminase, yielding oxaloacetic acid which oxidizes reduced β -nicotinamide adenine dinucleotide in the presence of malic dehydrogenase, resulting in a decrease in absorbance at 340 nm. The study samples were assayed in duplicate together with a series of 7 calibration standards containing *E coli* asparaginase in human serum at concentrations ranging from 0.025-0.25 IU/mL and 3 quality control samples with concentrations of 0.035, 0.12, and 0.22 IU/mL. Within-day accuracy of the assay, based upon determination of the quality control samples, ranged from 99.0 to 101.5% and the precision was 2.7 to 7.7%. Accuracy and precision for measuring asparaginase activity at the 0.025 U/mL lower limit of quantitation were 12.5% and 100.0%, respectively. NSAA 0.1 IU/mL was considered a therapeutic level based upon prior published data indicating that enzymatic activity at or above this threshold was associated with serum asparagine depletion.[18-23]

Statistical analysis

Descriptive statistics are presented with percentages where appropriate. The Fisher's exact test was used to test for association between categorical variables. The Wilcoxon rank sum test was used to assess differences in continuous variables between two groups. Event-free survival (EFS) was defined as the time from diagnosis to the first outcome event (induction failure, death during induction, death during remission or relapse). Because this analysis included only patients who were alive and in complete remission at the start of the intensification phase, a landmark approach defined at this time-point was used for all EFS estimates.

Results

Between September 2000 and December 2002, 215 children were enrolled on Protocol 00-01 and began the asparaginase intensification phase (week 7 of therapy) during which 30 weekly doses of *E coli* asparaginase were to be administered (Figure 1). Forty-five of these patients (21%) developed allergy to *E coli* asparaginase; 17 patients developed local allergy to the *E coli* preparation, 27 patients developed systemic allergy, and 1 had allergy of unknown severity. The median time from first post-induction dose of *E coli* asparaginase to the development of allergy was 5 weeks (range 1-24 weeks). Forty-two of the *E coli* asparaginase-allergic patients were switched to twice-weekly *Erwinia* asparaginase per protocol guidelines. The median age at diagnosis of *E coli*-allergic patients was 5 years (range, 1-17 years). There were no significant differences in presenting characteristics between patients who received *Erwinia* asparaginase due to *E coli* asparaginase allergy and those who did not develop *E coli* asparaginase allergy (Table I).

Toxicity

Fourteen of the 42 patients (33%) experienced a hypersensitivity reaction to *Erwinia* asparaginase (Table II). Five of the 14 patients experienced local reaction only and the other 9 patients experienced systemic hypersensitivity reactions, including generalized urticaria. Allergy to *Erwinia* asparaginase developed at a median of 8 weeks after switching to this

preparation (range, 2-15.5 weeks). All patients who developed *Erwinia* asparaginase allergy were switched to weekly IM PEG asparaginase.

Two of the 42 patients (5%) who switched to *Erwinia* asparaginase experienced severe pancreatitis while receiving *Erwinia*. These events occurred at 21.5 and 28 weeks after the first post-induction asparaginase dose, resulting in a permanent discontinuation of treatment with any type of asparaginase. One patient (2%) had mild pancreatitis while receiving *Erwinia* asparaginase, and resumed treatment with asparaginase after symptom resolution. One patient developed hyperglycemia requiring insulin. No cases of thrombosis were reported.

Ultimately, 34 of the 42 patients (81%) completed at least 26 total weeks of asparaginase intensification therapy, and 27 of the 42 patients (64%) completed all 30 planned weeks of planned asparaginase intensification. No significant difference in the total number of weeks of completed asparaginase therapy was found in a comparison between patients who did and did not develop *E coli* asparaginase allergy ($p=0.42$).

Nadir Serum Asparaginase Activity (NSAA) with *Erwinia* asparaginase

Samples for the determination of asparaginase activity were taken either 3 or 4 days after administration of a dose of *Erwinia* asparaginase, just prior to the next dose. Thirty-eight patients had at least one evaluable NSAA determination. Table III summarizes the NSAA results. The median NSAA of 88 samples obtained 3 days after the prior dose of *Erwinia* asparaginase was 0.247 IU/mL (range, <0.025-1.036 IU/mL), with 83% of the samples having an activity of at least 0.1 IU/mL. The median NSAA of 98 samples taken 4 days after dosing was 0.077 IU/mL (range, <0.025-0.757 IU/mL), with 42% above 0.1 IU/mL.

The median NSAA for the 14 patients who ultimately developed an allergic reaction to *Erwinia* asparaginase was 0.174 IU/mL (range <0.025-1.036 IU/mL), which was similar to the 24 patients who never developed *Erwinia* asparaginase allergy (median 0.135 IU/mL, range <0.025-0.927 IU/mL). Twelve of the 14 patients (86%) had at least one therapeutic NSAA determination (≥ 0.1 IU/mL) in the weeks prior to developing *Erwinia* asparaginase allergy.

Of the 38 *Erwinia*-treated patients with evaluable NSAA samples, 33 also had evaluable samples obtained during prior treatment with *E coli* asparaginase (prior to the development of allergy to *E coli* asparaginase and therefore prior to receiving *Erwinia* asparaginase). Only 14 of the 33 patients (42%) had at least one NSAA ≥ 0.1 IU/mL while receiving *E coli* asparaginase. In contrast, 34 of the 38 *E coli* asparaginase-allergic patients (89%) had at least one NSAA ≥ 0.1 IU/mL after switching to *Erwinia* asparaginase. Notably, samples with an NSAA ≥ 0.1 IU/mL were achieved during treatment with *Erwinia* asparaginase in 16 of the 19 patients (84%) who never had achieved a therapeutic NSAA level while receiving *E coli* asparaginase.

Event-Free Survival (EFS)

Of the 42 patients who developed allergy to *E coli* asparaginase and switched to *Erwinia* asparaginase, five relapsed and one died in remission as a consequence of sepsis. No second malignancies were observed. At a median follow-up of 5.4 years, EFS ($\pm$ standard error) for the 42 patients who switched to *Erwinia* asparaginase was $86 \pm 5\%$ in comparison to $81 \pm 3\%$ for the 170 patients without *E coli* asparaginase allergy ($p=0.55$ by the logrank test) (Figure 2).

Discussion

Asparaginase preparations derived from *E coli* are the most widely used forms of asparaginase and prior studies have highlighted their importance in the treatment of childhood ALL.[1,13,24,25] However, a significant percentage of patients develop allergic symptoms during treatment with native *E coli* asparaginase.[4-6] Previous studies have demonstrated that most patients with *E coli* asparaginase allergy also have a neutralizing antibody to the enzyme, resulting in sub-therapeutic systemic asparaginase activity even if allergic symptoms are prevented by the use of antihistamines and other premedications.[7,26-29] Thus, the development of allergy to *E coli* asparaginase requires a change to an alternative asparaginase preparation. Fewer patients may develop allergy and/or neutralizing antibodies to PEG asparaginase,[1,21] which is increasingly used in front-line therapy for ALL; however, hypersensitivity still occurs with this preparation, and when it does, a change to a noncross-reactive asparaginase preparation is necessary.

In this study, we demonstrated that twice-weekly *Erwinia* asparaginase was a tolerable and effective substitute in children and adolescents who developed *E coli* asparaginase allergy. Nearly all of these patients achieved a therapeutic NSAA (< 0.1 IU/mL) three days after an IM dose of *Erwinia* asparaginase. This included 16 of 19 patients (84%) who had never achieved therapeutic NSAA while being treated with *E coli* asparaginase, as well as 12 of 14 *E coli*-allergic patients (86%) who subsequently developed *Erwinia* asparaginase allergy. Despite the fact that all patients who received *Erwinia* asparaginase had a history of prior *E coli* asparaginase allergy, two-thirds (67%) did not develop allergy to *Erwinia* asparaginase. The frequency of pancreatitis in *Erwinia asparaginase*-treated patients (7%) was similar to what we typically observe on our trials in patients receiving 20-30 weeks of *E coli* or PEG asparaginase, and no thromboses were observed.[1,13] Importantly, there was no significant difference in EFS in children who received *Erwinia* asparaginase after *E coli* asparaginase allergy and those without a history of *E coli* asparaginase allergy, confirming previous reports that asparaginase hypersensitivity does not necessarily impact outcome of children with ALL.[2]

Since 1977, DFCI-ALL Consortium protocols have included an early intensification phase with 20-30 weeks of asparaginase.[1,13,25,30-32] We have found that the ability to tolerate asparaginase is an important predictor of outcome; on one study, patients who were able to receive 26 or more weeks of a planned 30-week treatment course of *E coli* asparaginase had superior EFS compared with patients who stopped asparaginase early due to toxicity.[1] The majority of patients reported here were able to complete all, or nearly all, of the planned treatment course of asparaginase despite experiencing allergy to *E coli* asparaginase; 81% of *E coli* allergic patients who were switched to *Erwinia* asparaginase completed at least 26 total weeks of asparaginase intensification therapy. Thus, the use of twice-weekly *Erwinia* asparaginase allowed *E coli* allergic patients to receive many more weeks of exposure to this important chemotherapeutic agent.

Erwinia asparaginase has a much shorter biological half-life of asparaginase activity (0.65 days) than either native *E coli* (1.44 days) or PEG asparaginase (5.73 days).[9] As a consequence, its administration schedule is an important variable in interpreting the results of clinical trials that include this agent. We have previously reported the results of a clinical trial (Protocol 95-01) in which children with ALL were randomized to receive either weekly *E coli* or weekly *Erwinia* asparaginase for 20 weeks during post-induction intensification. In that study, weekly *Erwinia* asparaginase was associated with a lower incidence of toxicity (10% versus 24%), but also with inferior 5-year EFS ($78 \pm 4\%$ versus $89 \pm 3\%$, $p=0.01$).[13] This result was likely due to the dosing schedule; with once-weekly dosing, it is probable that far fewer *Erwinia*-treated patients experienced continuous asparagine depletion during

the intensification phase compared with *E coli* asparaginase-treated patients. We demonstrate here that twice-weekly dosing of *Erwinia* asparaginase did not adversely impact EFS, suggesting that a more frequent dosing schedule is a more effective strategy for this agent.

The optimal dose and schedule of *Erwinia* asparaginase has not yet been determined. Results of pharmacokinetic studies in 15 newly diagnosed patients without previous asparaginase allergy indicated that administration of 8 doses of *Erwinia* asparaginase (at a dose of 10,000 IU/m²) given every 3 days during the induction phase of the AIEOP ALL-95 trial was associated with continuous asparagine depletion.[19] However, in a randomized trial conducted by the European Organization for Research and Treatment of Cancer (EORTC), *Erwinia* asparaginase given at the same dose and schedule was associated with higher induction failure and relapse rates compared with similarly dosed native *E coli* asparaginase. [24] Other reports suggest that higher doses and more frequent administration might be more effective. For example, higher NSAA and continuous asparagine depletion were observed in 21 children who received *Erwinia* asparaginase at a higher dose (20,000 IU/m²) and more frequently (three times weekly, with 2 and 3-day intervals between doses) as part of a Berlin-Frankfurt-Muenster (BFM) trial.[33] Also, an extremely high mean NSAA of 1.75 IU/mL was found in 27 patients receiving 10 daily doses of *Erwinia* asparaginase at a dose of 30,000 IU/m². [34] The impact of these dosing strategies on longterm outcome remains unclear.

The optimal dosing regimen for *Erwinia* asparaginase in patients with allergy to *E coli* asparaginase has not been established and information available from prior studies in this population remains limited.[18,27] Boos *et al.* reported on 16 patients who switched to twice-weekly *Erwinia* asparaginase (10,000 IU/m²) after allergy to native *E coli* asparaginase.[18] They found very low NSAA, with only one patient achieving a level 0.1 IU/mL, and a correspondingly low rate of plasma asparagine depletion (observed in only 3 patients). In contrast, we observed a much higher frequency of NSAA determinations above 0.1 IU/mL in our patients receiving twice-weekly *Erwinia* asparaginase. This difference may be due to the higher dose of *Erwinia* asparaginase (25,000 IU/m²) used in the present study.

Median NSAA levels after *Erwinia* asparaginase were higher 3 days after a dose compared with 4 days after a dose, with a greater percentage of 3-day levels at or above 0.1 IU/mL compared with 4-day levels. This suggests that dosing *Erwinia* asparaginase three times per week rather than twice-weekly might be a more efficacious strategy in terms of achieving continuous asparagine depletion. However, twice-weekly administration of *Erwinia* asparaginase is more convenient, reasonably well-tolerated, and did not appear to adversely impact EFS. Additional investigation will be necessary to determine whether more frequent dosing of *Erwinia* asparaginase is associated with a survival advantage compared with the twice-weekly schedule.

We conclude that switching to twice-weekly *Erwinia* asparaginase (at a dose of 25,000IU/m²) was effective and well-tolerated in patients with a history of *E coli* asparaginase allergy. *Erwinia* asparaginase should be considered as alternative therapy for children with ALL who develop allergy to *E coli*-derived asparaginase preparations.

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Figure 1.
Consort diagram.

Figure 2. Event-Free Survival. The 5.4-year EFS $\pm$ SE for *E coli* allergic patients switched to *Erwinia* asparaginase was $86 \pm 5\%$ compared with $81 \pm 3\%$ for those without asparaginase allergy ($p=0.55$).

Table I
Patient characteristics

	Received <i>Erwinia</i> after allergy to <i>E coli</i> asparaginase	No allergy to <i>E coli</i> asparaginase	<i>p</i>
No. of patients	42	170	
Age			
Median (years)	5.5	4	0.32
Range (years)	1-17	1-17	
10 years	13 (31%)	36 (21%)	
DFCI Risk Group			
SR	26 (62%)	100 (59%)	0.73
HR	16 (38%)	70 (41%)	
T-cell phenotype	6 (14%)	12 (7%)	0.08
WBC count (cells/ μ L)			
Median	9.8	13.5	
Range	1.2-252.2	1.5-320.7	0.21
<50,000	36 (86%)	158 (93%)	
50,000	6 (14%)	12 (7%)	
CNS-3 at diagnosis	0	4 (2%)	0.59
Down Syndrome	0	4 (2%)	0.59
Philadelphia chromosome	0	4 (2%)	0.59
MLL gene rearrangements	3 (7%)	7 (4%)	0.42

Values represent number of patients with percentage of the group in parentheses unless otherwise indicated.

Table II
Toxicities experienced by 42 patients receiving *Erwinia* asparaginase after *E coli* asparaginase allergy

	N
Developed <i>Erwinia</i> Allergy (switched to PEG)	14 (34%) [*]
Local reaction only	5
Systemic reaction	9
Moderate/Severe pancreatitis (stopped all asparaginase)	2 (5%) ^{**}
Mild pancreatitis (continued to receive asparaginase after recovery)	1 (2%)
Hyperglycemia (requiring insulin)	1 (2%)
Thrombosis/Bleeding	0 (0%)

^{*} Median time to *Erwinia* allergy 8 weeks, range 2-15.5 weeks;

^{**} Total weeks of ASP received: 21.5 and 28 weeks, respectively

Table III
Nadir Serum Asparaginase Activity (NSAA) in 38 patients who received *Erwinia* asparaginase after allergy to *E coli* asparaginase

	Number of samples	Median <i>Erwinia</i> asparaginase NSAA (range)	Percentage of post- <i>Erwinia</i> samples with NSAA 0.1 IU/mL
Day 3 NSAA	88	0.247 (<0.025-1.036)	83%
Day 4 NSAA	98	0.077 (<0.025-0.757)	42%