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The use of Erwinia Asparaginase for Adult Patients with Acute Lymphoblastic Leukemia after Pegaspargase Intolerance

Troy Z. Horvat[a], **Joshua J. Pecoraro**[a], **Ryan J. Daley**[a], **Larry W. Buie**[a], **Amber C. King**[a], **Raajit K. Rampal**[b], **Martin S. Tallman**[b], **Jae H. Park**[b], and **Dan Douer**[b]

[a]Department of Pharmacy, Memorial Sloan Kettering Cancer Center, New York, New York, USA

[b]Leukemia Service, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA

Abstract

Asparaginase administration has become a crucial component of front-line pediatric and pediatric inspired multi-agent regimens for the treatment of acute lymphoblastic leukemia (ALL). The aim of this study was to retrospectively assess the safety and feasibility of switching to Erwinia asparaginase after pegaspargase intolerance in adult ALL patients treated at Memorial Sloan Kettering Cancer Center. Our analysis included 10 patients, with a median age of 39 years (range 20–72), 90% males, 70% with B-cell ALL, and 30% with T-cell ALL. Nine patients were switched to Erwinia asparaginase after pegaspargase hypersensitivity and one patient after grade 4 hyperbilirubinemia secondary to pegaspargase. With Erwinia asparaginase, no hypersensitivity reactions occurred and no patient developed other known clinical asparaginase-related toxicities. Laboratory adverse effects consisted of mostly mild elevation in liver enzymes. No morphologic relapses have occurred in any patient switched to Erwinia asparaginase in first remission at a follow up of 0.4–34.6 months. These findings are unique in that all of our patients received Erwinia asparaginase after hypersensitivity or intolerance to pegaspargase and 50% of them were older than 40 years of age, a population with very limited data. Our observations provide preliminary information that treatment with Erwinia asparaginase can proceed as scheduled in adult patients, despite pegaspargase hypersensitivity and possibly liver intolerance.

Keywords

acute lymphoblastic leukemia; ALL; Erwinia asparaginase; pegaspargase; hypersensitivity; safety

Corresponding Author: Troy Z. Horvat[a] Department of Pharmacy, Memorial Sloan Kettering Cancer Center, 1275 York Ave, Schwartz 714, New York, NY 10065, Phone: 585-943-5111, horvatt@mskcc.org.
Dr. Horvat, Dr. Park, and Dr. Douer contributed equally to this article.

Introduction

In acute lymphoblastic leukemia (ALL), malignant lymphoblasts have reduced expression of the enzyme asparagine synthetase and are unable to produce adequate amounts of asparagine, an amino acid needed for cell survival. As a result, lymphoblasts depend on extracellular sources of asparagine to maintain protein biosynthesis. The therapeutic administration of asparaginase, an enzyme that hydrolyzes l-asparagine to ammonia and l-aspartic acid, is lethal to lymphoblasts.[1] As a result, prolonged asparaginase administration has become a crucial component of front-line pediatric and pediatric inspired multi-agent ALL regimens.[2–7]

Until recently, adult front-line regimens have either not included asparaginase or have only included it in 1–2 cycles.[8] However, more recent data in adults with an upper age limit ranging between 39 and 55 years shows that pediatric or pediatric inspired regimens, with more cumulative doses of asparaginase, increase event-free survival rates to 60–65%.[9–14]

Three forms of asparaginase have been used in clinical practice in the US: native asparaginase derived from Escherichia coli (Elspar®, Ovation Pharmaceuticals), a pegylated form of the native E. coli asparaginase (Oncaspar®, Sigma Tau Pharmaceuticals), and an enzyme isolated from Erwinia chrysanthemi, known as Erwinia asparaginase (Erwinaze®, Jazz Pharmaceuticals). Native asparaginase was removed from the US market in 2012, secondary to supply issues and continued manufacturing difficulties.[15]

One of the critical side effects of asparaginase is hypersensitivity, with a rate that varies from 1.8 to 9.4% of pegaspargase-treated patients.[11,14,16] Pegaspargase desensitization may not prevent recurrence of severe allergy; therefore patients should be switched to Erwinia asparaginase as a therapeutic alternative. [17] Erwinia-derived asparaginase also retains excellent activity in patients with E. coli asparaginase or pegaspargase neutralizing antibodies, and is deemed a suitable alternative for continued treatment in this patient population.[18–22]

Additional adverse effects warranting consideration of pegaspargase discontinuation include high-grade hepatotoxicity, pancreatitis, major thrombosis, and major bleeding. There appears to be a correlation between age and certain pegaspargase-related toxicities, particularly hepatotoxicity.[23,24]

The half-life of Erwinia asparaginase is 7.5 hours (intravenous) or 15.6 hours (intramuscular), much shorter than that of pegaspargase (5.7–7 days).[25–27] Although currently not recommended, in patients with prior non-allergic severe toxicity to pegaspargase, Erwinia asparaginase might also be considered as a therapeutic alternative. Erwinia asparaginase has a significantly reduced duration of action that permits tighter control of drug exposure and more rapid reversal of asparagine depletion, should adverse effects occur. Nevertheless, the risk for allergic and non-allergic asparaginase-related adverse effects does still exist with the use of Erwinia asparaginase. The aim of this study was to assess the safety and feasibility of switching to Erwinia asparaginase in adult ALL patients after pegaspargase hypersensitivity or severe toxicity.

Methods

This is a single-center retrospective analysis of ten adult ALL patients who were switched to Erwinia asparaginase after allergy or intolerance to pegaspargase between November 2011 and May 2016. Toxicities were graded using the Common Terminology Criteria for Adverse Events version 4.0. The Memorial Sloan Kettering Cancer Center Investigational Review Board granted an exemption from IRB review.

Results

Patient characteristics

Ten adult patients received a total of 35 cycles (median 4 cycles each, range 1–6) of Erwinia asparaginase given as part of various pediatric-inspired chemotherapy regimens. The median age was 39 years (range 20–72), 90% were male, 70% had B-cell ALL, and 30% had T-cell ALL. Nine patients received Erwinia asparaginase while in first complete remission and only one as part of second-line therapy.

Patients received a median of 2 prior doses of pegaspargase (range 1–4) before switching to Erwinia asparaginase. The reasons for switching to Erwinia asparaginase were grade 3/4 pegaspargase-related clinical hypersensitivity in 9 patients (anaphylaxis n=7, urticaria/pruritus n=2) and grade 4 hyperbilirubinemia in one patient. A summary of patient characteristics is shown in table 1.

Erwinia asparaginase dosing

Each cycle consisted of Erwinia asparaginase 25,000 units/m^2 intramuscularly every 48 hours for 6 doses (either including or excluding weekends). Hydrocortisone 50–100 mg IV premedication was given with 66 of 203 total Erwinia asparaginase doses. Additionally, acetaminophen 650 mg and diphenhydramine 25–50 mg were given with 83 and 107 of 203 total Erwinia asparaginase doses, respectively. Seven patients received all intended doses of Erwinia asparaginase, 1 patient was lost to follow up after 1 cycle, and 2 patients were still receiving treatment at the time of analysis.

Erwinia asparaginase-related toxicities and patient outcome

No hypersensitivity reactions occurred and no patient developed other known clinical asparaginase- related toxicities. Laboratory adverse effects are reported in table 2 and consisted of mostly mild elevation in liver enzymes. The single patient who received Erwinia asparaginase as part of second-line therapy died from disease progression. Additionally, one patient died in a motor vehicle accident while in first complete remission. The remaining eight patients are alive and in first remission at 3.0–56.3 months from diagnosis. No morphologic or molecular relapses have occurred in any patient treated in first remission at a follow up of 0.4–34.6 months after switching to Erwinia asparaginase. No patient had undergone allogeneic hematopoietic stem cell transplant at the time of analysis.

Discussion

We analyzed 10 patients to assess the safety and feasibility of using Erwinia asparaginase in adult ALL patients, nine after previous pegaspargase hypersensitivity. Replacing pegaspargase with Erwinia asparaginase after hypersensitivity allowed all patients to complete asparaginase therapy without hypersensitivity. Currently hypersensitivity is the only recommended reason, as well as the only FDA approved indication, for switching to Erwinia asparaginase.[28] Nevertheless, one patient was switched to Erwinia asparaginase after grade 4 hyperbilirubinemia with pegaspargase. This patient was able to receive 24 doses of Erwinia asparaginase with only a grade 2 hyperbilirubinemia. This was transient and caused no adverse clinical consequences.

In general, adverse effects with Erwinia asparaginase were limited to laboratory abnormalities of minimal clinical consequence. In contrast to the known high rate of hepatotoxicity in adults treated with pegaspargase, in particular hyperbilirubinemia of 16–24%[9,16,24] none of our patients developed grade 3 or 4 hyperbilirubinemia and only one patient had a grade 3 elevation in alanine aminotransferase. Within our small cohort undergoing first-line therapy, relapse did not occur after transitioning to this therapeutic alternative, although follow up was short in some patients.

Data for the use of Erwinia asparaginase in adult patients are lacking, particularly in those over the age of 40 years. The findings of a large compassionate-use trial established the safety profile of Erwinia asparaginase in children, adolescents and younger adults with ALL or lymphoblastic lymphoma, who had experienced hypersensitivity reactions to E. coli-derived asparaginase.[22] However, only nine patients over the age of 40 were enrolled in this study. Bigliardi and colleagues reported positive results in treating adult patients with Erwinia asparaginase in the front-line setting, however, only three of their eleven patients treated with Erwinia asparaginase were over the age of 40.[29] Our data are unique in that all of our patients received Erwinia asparaginase after hypersensitivity or intolerance to pegaspargase and 50% of them were older than 40 years of age.

Limitations of our analysis include: a single institution experience, a relatively small sample size, and retrospective grading of toxicity. Additionally, data on asparaginase trough levels and serum asparagine depletion were not available. However, our patients received Erwinia asparaginase via the intramuscular route which was reported to produce adequate asparaginase activity between doses in all patients as compared to the intravenous route.[30] Additionally, no patients experienced pegaspargase-pancreatitis, major thrombosis, or major hemorrhage. However, due to the small sample size of our analysis, no comments can be made about the rates and safety of continuing Erwinia asparaginase after these toxicities. The results from the analysis of our relatively small cohort should be confirmed with larger prospective cohorts.

The completion of all planned asparaginase treatments has been shown to be clinically beneficial in the pediatric ALL population.[18] In light of the critical role of asparaginase in ALL therapy, our observations, along with pediatric and young adult data,[22,29] provides

preliminary information that treatment with Erwinia asparaginase can proceed as scheduled despite pegaspargase hypersensitivity and possibly liver intolerance.

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Highlights

- Ten patients were switched to Erwinia asparaginase after pegaspargase intolerance
- After switching to Erwinia asparaginase, no hypersensitivity reactions occurred
- No patient developed clinically relevant asparaginase-related toxicities
- No relapses occurred in patients switched to Erwinia asparaginase in CR1
- Erwinia asparaginase can administered, despite prior pegaspargase intolerance

Table 1

Patient Characteristics

Pt	Age/ Sex	Diagnosis	Regimen	Number of prior lines of therapy	Number of doses of Peg received prior to switching	Remission status prior to receiving Erwinia	Reason for change	Number of Erwinia cycles
1	29/M	T-ALL	C10403	0	2	Morpholo gic CR (MRD not assessed)	SOB, chest discomfort, flushing, facial/throat swelling	5
2	23/M	B-ALL	AALL07P1	1	2	MRD+CR	Anaphylaxis	4
3	20/M	B-ALL	NYII	0	3	MRD negative CR	Hypotensio n, SOB, facial swelling	6
4	59/M	T-ALL	MSKCC 12-266	0	4	MRD negative CR	Rash, Hives, SOB	3
5	28/M	B-ALL	MSKCC 12-266	0	2	MRD negative CR	Hypotensio n, diaphoresis, tachycardia, and nausea	4
6	72/F	B-ALL	MSKCC 12-266	0	1	MRD negative CR	SOB, flushing, rash	1
7	33/M	B-ALL	MSKCC 12-266	0	2	MRD negative CR	Tachycardia, hypotension , syncope, LOC	5
8	55/M	B-ALL	MSKCC 12-266	0	1	Morpholo gic CR (MRD not assessed)	Hepatotoxic ity with grade 4 hyperbilirub inemia	4
9	44/M	B-ALL	MSKCC 12-266	0	2	MRD negative CR	SOB, blurred vision, diaphoresis	3 *
10	54/M	T-ALL	MSKCC 12-266	0	2	MRD negative CR	Hypotensio n, tachycardia, flushing, hives	1 *

AST median (range)	ALT median (range)	Tbili median (range)	Amylase median (range)	Lipase median (range)	TG median (range)	Fibrinogen median (range)	Thrombosis/ Hemorrhage	Hypersensitivity to Erwinia
23 (16–57)	44 (23–102)	0.4 (0.2–0.7)	33 (29–39)	16 (11–25)	288 (189–683)	231 (144–305)	No/No	No
35 (22–56)	66 (29–70)	0.6 (0.6–0.9)	37 (28–50)	NR	NR	149 (106–335)	No/No	No
57 (40–60)	77 (59–112)	0.9 (0.6–1)	28 (23–53)	NR	NR	137 (77–176)	No/No	No
19 (16–38)	24 (14–44)	0.5 (0.2–0.9)	45 (27–55)	34 (30–49)	159 (93–318)	311 (206–440)	No/No	No
29 (16–57)	41 (22–69)	0.4 (0.2–0.8)	66 (56–131)	34 (23–47)	246 (80–819)	170 (102–247)	No/No	No
33 (21–36)	53 (40–54)	0.3 (0.3–0.4)	36 (29–36)	35 (29–37)	196 (195–330)	219 (219–325)	No/No	No
26 (13–72)	59 (36–157)	0.6 (0.4–1.0)	76 (35–102)	47 (30–84)	839 (144–2180)	180 (128–276)	No/No	No
26 (16–109)	25 (14–99)	1.0 (0.7–1.3)	74 (51–102)	30 (23–54)	200 (67–386)	186 (134–309)	No/No	No
9 (7–20)	12 (11–16)	0.5 (0.4–0.7)	12 (8–16)	24 (23–61)	535 (167–2076)	185 (178–207)	No/No	No
87 (64–119)	128 (68–243)	0.4 (0.3–0.7)	71 (51–84)	61 (41–70)	446 (380–667)	158 (125–245)	No/No	No

Pt = Patient; Peg = Pegaspargase; M = male; F = female; T-ALL = T-cell acute lymphoblastic leukemia; B-ALL = B-cell acute lymphoblastic leukemia; C10403 = CALBG 10403 protocol; CR = complete remission; MRD = minimal residual disease; MSKCC 12-266 = A Berlin-Frankfurt-Munster modeled, pediatric inspired multiagent chemotherapy regimen for newly diagnosed patients with ALL (NCT01920737); SOB = Shortness of breath; LOC = Loss of consciousness;

* = Patients still receiving treatment;

AST = Aspartate transaminase; ALT = Alanine transaminase; Tbili = Total bilirubin; TG = triglycerides

Table 2

Laboratory abnormalities by grade

	Grade 1	Grade 2	Grade 3	Grade 4
AST	7	1	0	0
ALT	7	2	1	0
TBILI	1	1	0	0
Amylase	3	0	0	0
Lipase	3	1	0	0
Triglycerides	4	4	5	2
Fibrinogen	3	7	1	0
Total	28	16	7	2