Leukemia Research 50 (2016) 17–20

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

The use of Erwinia asparaginase for adult patients with acute lymphoblastic leukemia after pegaspargase intolerance

Troy Z. Horvat[a,*,1], 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,1], Dan Douer[b,1]

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

ARTICLE INFO

Article history:
Received 8 June 2016
Received in revised form 1 August 2016
Accepted 26 August 2016
Available online 26 August 2016

Keywords:
Acute lymphoblastic leukemia
ALL
Erwinia asparaginase
Pegaspargase
Hypersensitivity
Safety

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 retrospective study was to 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), male predominance (90%), and a typical B-cell to T-cell ratio (70:30%) for 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 Erwinia asparaginase 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.

1. 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 and has become a crucial component of front-line pediatric and pediatric-inspired multi-agent ALL regimens [1–7].

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 higher cumulative doses of asparaginase, increase event-free survival rates to 55%–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 U.S. 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

* Corresponding author at: Department of Pharmacy, Memorial Sloan Kettering Cancer Center, 1275 York Ave., Schwartz 714, New York, NY 10065, USA.
E-mail addresses: horvatt@mskcc.org (T.Z. Horvat), Pecorarj@mskcc.org (J.J. Pecoraro), daleyr@mskcc.org (R.J. Daley), buiel@mskcc.org (L.W. Buie), kinga@mskcc.org (A.C. King), rampalr@mskcc.org (R.K. Rampal), TallmanM@mskcc.org (M.S. Tallman), ParkJ6@mskcc.org (J.H. Park), Douer_d@med.usc.edu (D. Douer).
[1] These authors contributed equally to this article.

http://dx.doi.org/10.1016/j.leukres.2016.08.014
0145-2126/

Table 1
Baseline Characteristics: 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.

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	Morphologic CR (MRD not assessed)	SOB, chest discomfort, flushing, facial/throat swelling	5
2	23/M	B-ALL	AALL07P1	1	2	MRD positive CR	Anaphylaxis	4
3	20/M	B-ALL	NYII	0	3	MRD negative CR	Hypotension, 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	Hypotension, 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	Morphologic CR (MRD not assessed)	Hepatotoxicity with grade 4 hyperbilirubinemia	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	Hypotension, tachycardia, flushing, hives	1*

Table 2
Laboratory and Clinical Parameters During Erwinia Asparaginase Treatment. AST = Aspartate transaminase; ALT = Alanine transaminase; Tbili = Total bilirubin; TG = triglycerides.

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

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 h (intravenous) or 15.6 h (intramuscular), much shorter than that of pegaspargase (5.7–7 days) [25–27]. Although currently not routinely recommended, in patients with prior non-allergic severe toxicity to pegaspargase, Erwinia asparaginase may also be considered as a therapeutic alternative. Erwinia asparaginase has a significantly reduced duration of action that permits tighter control of drug exposure 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.

2. 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.

3. Results

3.1. 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