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Research paper

Pegaspargase-related high-grade hepatotoxicity in a pediatric-inspired adult acute lymphoblastic leukemia regimen does not predict recurrent hepatotoxicity with subsequent doses

Patrick W. Burke[a,*], Ibrahim Aldoss[b], Matthew A. Lunning[c], Sean M. Devlin[d], Martin S. Tallman[e], Vinod Pullarkat[b], Ann M. Mohrbacher[f], Dan Douer[f]

[a] Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan, Michigan Medicine, F4811D University Hospital South, 1500 East Medical Center Drive, SPC 5271, Ann Arbor, MI, 48109-5000, United States
[b] Department of Hematology and Hematopoietic Cell Transplantation, City of Hope Medical Center, Duarte, CA, United States
[c] Division of Oncology and Hematology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, United States
[d] Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, United States
[e] Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, United States
[f] Division of Hematology, University of Southern California, Los Angeles, CA, United States

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ABSTRACT

Pediatric acute lymphoblastic leukemia (ALL) regimens, including higher cumulative asparaginase doses, have been investigated in adult ALL to improve outcomes. Preliminary results are promising, but hepatotoxicity rates with long-acting pegaspargase are greater in adults than children. However, adult pegaspargase-related hepatotoxicity is not as clearly defined despite being the commonest adult toxicity. We studied the frequency and characteristics of high-grade pegaspargase-related hepatotoxicity in newly diagnosed adults on a pediatric-inspired regimen that included six planned pegaspargase doses, 2000 IU/m^2/dose intravenously, with doses given at least four weeks apart and not discontinued or dose-reduced for previous hepatotoxicity. Pegaspargase-related toxicity was monitored weekly after 185 delivered doses and reported by NCI CTCAE v3.0. Fifty-one patients, aged 18–57, received 192 pegaspargase doses (3.8 doses/patient). High-grade hyperbilirubinemia occurred in 16 (31.4%) patients and 23 (12.4%) doses; high-grade transaminitis occurred in 33 (64.7%) patients and 62 (33.5%) doses. Of 11 patients with high-grade hyperbilirubinemia who received at least one subsequent pegaspargase dose, six (54.5%) experienced recurrent toxicity; of 24 patients with high-grade transaminitis who received at least one subsequent pegaspargase dose, 15 (62.5%) developed recurrent toxicity. Pegaspargase at this dose and interval is associated with high hepatotoxicity rates, but patients can be rechallenged despite earlier pegaspargase-related hepatotoxicity.

1. Introduction

Outcomes in pediatric acute lymphoblastic leukemia (ALL) have markedly improved, with an approximate 80% cure rate now [1–4]. In adult ALL, however, 90% of patients achieve a complete remission (CR), but most eventually relapse, and only 40% sustain long-term remission [1,5–13].

Among suggested reasons for this outcome discrepancy are differences in chemotherapy delivery–dose intensity and density–particularly when addressing toxicity [14]. Pediatric ALL regimens also emphasize higher doses of non-myelosuppressive chemotherapy, e.g., vincristine, corticosteroids and, notably, higher cumulative doses of asparaginase [14–18]. All pediatric ALL regimens incorporate asparaginase, while toxicity concerns previously limited adult asparaginase use.

Recently, several adult ALL studies used true pediatric or "pediatric-inspired" protocols, which all included high cumulative asparaginase doses, and reported promising preliminary results [19–24]. Some of these adult studies employed multiple doses of the long-acting *E. coli* L-asparaginase, pegaspargase, and observed high-grade hepatotoxicity rates greater than reported in children or for the native *E. coli* L-asparaginase. In fact, high-grade hepatotoxicity has emerged as the commonest adult pegaspargase adverse effect but has not yet been well characterized in adults [23,25–38]. Improved outcomes in these studies and unavailability of the native enzyme in the United States will likely

* Corresponding author.
E-mail address: pwburke@med.umich.edu (P.W. Burke).

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increase pegaspargase adult use, generating more patients with hepatotoxicity.

We recently reported results of our "pediatric-inspired" ALL regimen in adults that includes multiple pegaspargase doses (NCT00184041) [33,34]. We herein report a more detailed retrospective analysis regarding the frequency and characteristics of pegaspargase-related high-grade hepatotoxicity observed in this study.

2. Methods

2.1. Patients

Patients enrolled on the phase II trial at the University of Southern California (USC). Patients were excluded pretreatment for severe hepatic dysfunction: serum bilirubin > two times Institutional Upper Limit of Normal (IULN) or serum transaminitis–aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > three times IULN, unless hepatic dysfunction was ascribed to ALL. Other eligibility requirements were previously reported [33,34].

2.2. Treatment protocol

Regimen details were previously published (Supplemental Figs. 1, 2) [33,34]. Briefly, a pediatric-inspired adult ALL regimen included a two-phase Induction. Patients achieving CR [8,34] proceeded with three post-induction cycles (Intensification, Consolidation, and Delayed Re-Induction) repeated once in succession, for a total of six post-induction cycles [33,34]. Subsequently, patients received a two-year Maintenance. Six pegaspargase doses at 2000 International Units per meter squared per dose (IU/m^2/dose) uncapped intravenously were scheduled, with one dose each in: Induction Phase I (IND1), Induction Phase II (IND2), Intensification I (INT1), Delayed Re-Induction I (DRI1), Intensification II (INT2), and Delayed Re-Induction II (DRI2). Intervals between pegaspargase doses were four weeks minimum. No dose reduction or discontinuation was permitted for hepatotoxicity.

Beginning in 2007, imatinib 600 milligrams daily was added for Philadelphia chromosome-positive patients. Patients did not receive azoles, antibacterial prophylaxis, or sulfamethoxazole-trimethoprim anti-*Pneumocystis jirovecii* prophylaxis. Anecdotal case reports show successful treatment of asparaginase-related hepatotoxicity with levocarnitine [39]. However, neither levocarnitine nor ursodiol were used for prophylaxis or treatment.

This trial was conducted in accordance with the ethical standards of the USC Institutional Review Board and the Helsinki Declaration of 1975, as revised in 2000.

2.3. Statistics

Pegaspargase-related toxicities were closely monitored weekly following each pegaspargase dose–using history, physical exam, and laboratory assessments–and reported using NCI CTCAE v3.0. Hepatic synthetic function assessments, including serum albumin, aPTT, PT/INR, and plasma fibrinogen, were monitored but not included in the current report due to incomplete data. Hyperbilirubinemia was defined using serum total bilirubin. High-grade hepatotoxicity was defined as grade 3/4.

Fisher's exact tests and *t*-test were used to compare baseline characteristics for patients with and without high-grade hepatotoxicities. The average number of subsequent pegaspargase doses for patients with and without hyperbilirubinemia and/or transaminitis toxicities were compared using a *t*-test at selected treatment cycles. To investigate whether patients with IND1 toxicities are at higher risk of toxicities in IND2 or later, Fisher's exact was used to compare the proportion with later toxicities for patients with and without IND1 toxicities. All analyses were conducted using the R statistical package.

3. Results

3.1. Pegaspargase delivery

Fifty-one patients, aged 18–57 years, enrolled and received 192 pegaspargase doses (3.8 doses/patient); 23 (45.1%) patients received all six planned doses. The remaining 28 patients received: four (n = 1), three (n = 7), two (n = 9), and one (n = 11) pegaspargase doses. No patient discontinued due to pegaspargase-related hepatotoxicity [35]. Pegaspargase-related toxicity data was available for 185 doses (3.6 doses analyzed/patient).

3.2. Baseline patient characteristics

High-grade hyperbilirubinemia or transaminitis developed in 16 (31.4%) and 33 (64.7%) patients, respectively. Eighteen (35.3%) patients never developed high-grade hepatotoxicity. There were no significant statistical differences between the groups (Table 1).

3.3. High-grade hepatotoxicity and pegaspargase delivery

Among 185 analyzable pegaspargase doses, high-grade hyperbilirubinemia occurred after 23 (12.4%) doses, and high-grade transaminitis manifested after 62 (33.5%) doses. All 16 patients with high-grade hyperbilirubinemia also experienced at least one high-grade

Table 1
Baseline patient characteristics.

		No Grade 3/4 Hepatotoxicity	Grade 3/4 Hepatotoxicity			
			Bilirubinemia	P[c]	Transaminitis	P[c]
Patients, N (%)[a]		18 (35.3%)	16 (31.4%)		33 (64.7%)	
Toxic Doses, N (%)[b]		0 (0%)	23 (12.4%)		62 (33.5%)	
Age, Yrs, Median (range)		30.5 (18–57)	39 (21–57)	0.16	33 (19–57)	0.32
Female, N (%)		5 (27.8%)	6 (37.5%)	0.72	13 (39.4%)	0.54
BMI, Kg/M^2, Mean (range)		25.2 (20.2–30.7)	27.8 (21.6–33.8)	0.055	27.7 (21.6–35.2)	0.065
Presenting WBC/μL, Median (range)		15,600 (3100–352,000)	13,000 (800–135,700)	0.43	10,100 (800–512,000)	0.53
Risk, N (%)	Stand	7 (38.9%)	4 (25.0%)	0.48	9 (27.3%)	0.49
	High	11 (61.1%)	12 (75.0%)		24 (72.7%)	
Phenotype, N (%)	B-Cell	16 (88.9%)	16 (100%)	0.49	30 (90.9%)	0.99
	T-Cell	2 (11.1%)	0 (0%)		3 (9.1%)	
Ph+, N (%)		6 (33.3%)	3 (18.8%)	0.45	5 (15.2%)	0.16

Abbreviations: BMI = Body Mass Index. Stand = Standard. Ph+ = Philadelphia Chromosome-Positive. P = P Value.

[a] Based on 51 patients.

[b] Based on 185 pegaspargase doses evaluable for toxicity.

[c] Fisher's exact tests and *t*-test compare baseline characteristics for patients with hyperbilirubinemia or transaminitis to patients without liver toxicities at any point during the treatment regimen.