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Brief report

Intravenous PEG-asparaginase during remission induction in children and adolescents with newly diagnosed acute lymphoblastic leukemia

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Over the past several decades, L-asparaginase, an important component of therapy for acute lymphoblastic leukemia (ALL), has typically been administered intramuscularly rather than intravenously in North America because of concerns regarding anaphylaxis. We evaluated the feasibility of giving polyethylene glycosylated (PEG)–asparaginase, the polyethylene glycol conjugate of *Escherichia coli* L-asparaginase, by intravenous infusion in children with ALL. Between 2005 and 2007, 197 patients (age, 1-17 years) were enrolled on Dana-Farber Cancer Institute ALL Consortium Protocol 05-01 and received a single dose of intravenous PEG-asparaginase (2500 IU/m^2) over 1 hour during remission induction. Serum asparaginase activity more than 0.1 IU/mL was detected in 95%, 88%, and 7% of patients at 11, 18, and 25 days after dosing, respectively. Toxicities included allergy (1.5%), venous thrombosis (2%), and pancreatitis (4.6%). We conclude that intravenous administration of PEG-asparaginase is tolerable in children with ALL, and potentially therapeutic enzyme activity is maintained for at least 2 weeks after a single dose in most patients. This trial was registered at www.clinicaltrials.gov as #NCT00400946. (Blood. 2010;115:1351-1353)

Introduction

Asparaginase is an important and universal component of therapy for childhood acute lymphoblastic leukemia (ALL). Since 1977, the Dana-Farber Cancer Institute ALL Consortium has included 20 to 30 consecutive weeks of asparaginase during postinduction consolidation therapy and has demonstrated that this treatment significantly improves long-term event-free survival.[1,2] Asparaginase preparations are bacterially derived and, therefore, have the potential to be highly immunogenic. Hypersensitivity reactions to asparaginase occur in up to 30% of patients and are frequently associated with the development of neutralizing antibodies.[3] Other asparaginase-associated toxicities include pancreatitis (in 5%-10% of patients) and thrombosis (in 2%-5% of patients).[4,5] Patients who receive a truncated course of asparaginase because of intolerable side effects may have an inferior outcome compared with those who receive all intended doses.[4]

Polyethylene glycosylated (PEG)–asparaginase, formed by covalently attaching polyethylene glycol to the native *Escherichia coli* enzyme, was developed with the objective of reducing the immunogenic potential. When given intramuscularly, PEG-asparaginase has a longer half-life and is associated with a lower rate of antibody formation than the native enzyme.[6,7] All asparaginase preparations have typically been administered intramuscularly rather than intravenously in North America because of concerns about the risk of anaphylaxis. Considering that many pediatric patients have indwelling venous catheters, intravenous administration would be a more convenient and less painful option for dosing than intramuscular injection. Published information pertaining to the clinical experience with intravenous PEG-asparaginase in pediatric patients is limited. In this report, we describe the toxicity and pharmacokinetics of a single dose of intravenous PEG-asparaginase given during induction therapy to 197 children with newly diagnosed ALL.

Methods

Patients

Between May 2005 and May 2007, 197 evaluable patients between the ages of 1 and 18 years with newly diagnosed ALL were enrolled in the Dana-Farber Cancer Institute ALL Consortium Protocol 05-01 (National Clinical Trial Reference #00400946: Pegasparaginase or Asparaginase and

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Table 1. Serum asparaginase activity after a single dose of PEG-asparaginase (2500 IU/m^2) given as a 1-hour intravenous infusion in children and adolescents with newly diagnosed ALL

		Serum asparaginase activity, IU/mL		Percentage of patients with asparaginase activity, IU/mL		
Sample time, d	No. of patients	Median (range)	Mean ± SD	≥ 0.025	≥ 0.1	≥ 0.2
4	130	0.66 (< 0.025-2.34)	0.73 ± 0.29	96	96	96
11	133	0.48 (< 0.025-1.58)	0.49 ± 0.22	97	95	92
18	112	0.20 (< 0.025-1.24)	0.23 ± 0.14	96	88	52
25	113	0.04 (< 0.025-0.41)	0.07 ± 0.05	70	7	2

Combination Chemotherapy in Treating Young Patients With Newly Diagnosed Acute Lymphoblastic Leukemia). The Institutional Review Boards at each participating institution approved the protocol before patient enrollment. Informed consent was obtained from parents or guardians before starting therapy in accordance with the Declaration of Helsinki.

Treatment

Patients were classified as standard or high risk according to pretreatment criteria, as previously described.[8] For all patients, remission induction commenced with 3 days of methylprednisolone followed by 28 days of multiagent therapy, including weekly vincristine, daily prednisone (or methylprednisolone), 2 doses of doxorubicin, and low-dose methotrexate. On day 7, all patients received one dose of PEG-asparaginase (2500 IU/m^2) administered intravenously over 1 hour.

Toxicity

Toxicity data were collected prospectively. All toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0. All cases of thrombosis were radiographically confirmed. Because grade 2 pancreatitis (episodes without surgical intervention or life-threatening consequences) can encompass a wide range of clinical severity, we further classified these cases based on duration of clinical signs/symptoms: mild/moderate (< 72 hours in duration) or severe (≥ 72 hours).

Pharmacokinetic studies

Serum was harvested from peripheral blood samples obtained before intravenous PEG-asparaginase and 4, 11, 18, and 25 days after its administration. Asparaginase activity was determined by a validated biochemical assay with a 0.025 IU/mL lower limit of quantitation as previously reported.[9] A one-compartment open model with Michaelis-Menton elimination was fit to the mean serum asparaginase activity versus time data by nonlinear regression as previously described.[10]

Statistical analysis

Asparaginase activity data at the specified time points plus or minus 1 day were analyzed descriptively. Samples with enzyme activity less than 0.025 IU/mL were excluded from calculations of the mean and SD. A mixed model for repeated measures adjusted for age, sex, and leukocyte count at diagnosis was constructed to test for differences in the log-transformed asparaginase activity. *P* values are 2-sided with values less than .05 considered statistically significant.

Results and discussion

Age at diagnosis ranged from 1 to 17 years (median, 5 years). A total of 87% had precursor B-cell phenotype and 13% T-ALL. A total of 58% were classified as standard risk and 42% high risk.

Asparaginase activity was determined in serum samples obtained from 186 patients. Measurable serum asparaginase activity was observed in 96% of patients 18 days after a single dose of intravenous PEG-asparaginase (Table 1). In the adjusted mixed model, there were no statistically significant differences in serum asparaginase activity over time based on age ($P = .11$), sex ($P = .90$), or white blood cell count at diagnosis ($P = .78$).

The time course of the mean asparaginase activity is shown in Figure 1. The pronounced negative departure from log-linear decay of the enzymatic activity over time is characteristic of a saturable elimination process. A pharmacokinetic model with Michaelis-Menten elimination yielded an excellent fit of the mean serum asparaginase activity-time data, whereas a model with first-order monoexponential elimination did not describe the data particularly well. This is entirely consistent with the findings described in other pediatric studies of intravenous PEG-asparaginase.[10,11] Moreover, there were no discernable differences between the time course of serum enzymatic activity after intravenous administration of PEG-asparaginase and that reported in other studies in which PEG-asparaginase was given by the intramuscular route.[6,7]

Many investigators consider that continuously maintaining serum asparaginase activity more than 0.1 IU/mL is necessary for optimal serum asparagine depletion and therapeutic effectiveness.[12] We observed that 88% of patients had serum asparaginase activity at or above 0.1 IU/mL for 18 days after dosing, but only 7% maintained this level of activity after 25 days (Table 1). Other investigators have suggested that continuous exposure to a higher enzyme activity (ie, ≥ 0.2 IU/mL) may be therapeutically beneficial.[11] More than 90% of patients had an enzyme activity at or above 0.2 IU/mL for 11 days after dosing, and 52% had this level after 18 days. Thus, using either criterion, our findings suggest that

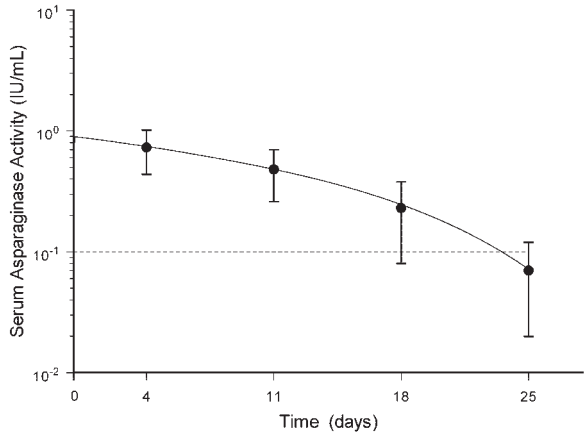

Figure 1. Time course of the mean serum asparaginase activity. Data points depicting the mean of the assayed values for samples collected from all patients at each time point are shown; error bars represent SD. The solid curve was generated by fitting the differential equation, $dA_s/dt = (I - CL \times A_s)/V$, to the mean serum asparaginase activity (A_s) versus time (t) data. The value of the drug input function (I) was defined as *dose/infusion duration* during drug administration and as 0 at all other times. CL (total body clearance) = $V_m/(K_m + A_s)$, where V_m and K_m are the maximum metabolic capacity and Michaelis-Menten constant, respectively; V is the apparent volume of distribution. Estimated values of the iterated parameters were V_m = 124 IU/h per m^2 and K_m = 0.110 IU/mL, V = 2.79 L/m^2.

a single 2500-IU/m^2 dose of intravenous PEG-asparaginase probably provides therapeutically effective serum enzyme activity in most patients for 2 weeks and for some patients even longer.

The single dose of intravenous PEG-asparaginase was reasonably well tolerated. The most common asparaginase-related toxicity was pancreatitis, observed in 9 (4.5%) patients (1 grade 1, 7 mild/moderate grade 2, and 1 severe grade 2). Pancreatitis developed 0 to 26 days after dosing (median, 13 days). Four patients (2%) developed a thrombotic complication, including 2 in the central nervous system (diagnosed 18 and 25 days after dose) and 2 non-central nervous system (14 and 25 days after dose). There was one case of hypertriglyceridemia (grade 4, 27 days after dose), and there were no asparaginase-related deaths. These toxicity rates are similar to those reported for children with ALL after a single dose of intramuscular PEG during remission induction.[7] Asparaginase-related complications occurred in 6% of patients 1 to 10 years of age and 14% of those 10 years or older at diagnosis ($P = .13$).

Hypersensitivity occurred in 3 patients (1.5%), all during the infusion. One episode was grade 2, and 2 were grade 3. It remains to be determined how intravenous administration affects antibody formation and allergy rates with reexposure to asparaginase during subsequent treatment phases. We have previously reported that every 2-week intramuscular PEG-asparaginase was associated with a lower rate of allergy compared with weekly intramuscular *E coli* asparaginase during a 30-week consolidation phase.[4]

In conclusion, the intravenous administration of PEG-asparaginase is feasible and well tolerated in children with ALL. A therapeutically effective serum enzyme activity is maintained in nearly all patients for at least 2 weeks after a single dose of 2500 IU/m^2. We are currently comparing the relative toxicity and efficacy of intravenous PEG-asparaginase (given every 2 weeks) and intramuscular *E coli* asparaginase (given weekly) for 30 weeks during the postinduction consolidation phase of therapy.

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Authorship

Contribution: L.B.S. designed research, performed research, analyzed and interpreted data, and wrote the manuscript; J.G.S. contributed vital analytic tools, performed research, analyzed and interpreted data, and wrote the manuscript; K.E.S. and D.S.N. analyzed and interpreted data and performed statistical analyses; C.W. and J.E.O. collected data and edited the manuscript; L.M.V., B.L.A., U.H.A., L.C., P.D.C., K.M.K., C.L., B.M., M.S., and C.L.S. performed research and edited the manuscript; H.J.C. analyzed and interpreted data and edited the manuscript; and S.E.S. designed research and edited the manuscript.

Conflict-of-interest disclosure: L.B.S. received honoraria for speaking engagements from Enzon Pharmaceuticals. J.G.S. received research funding from Enzon Pharmaceuticals. S.E.S. received honoraria for speaking engagements and research funding from Enzon Pharmaceuticals. The remaining authors declare no competing financial interests.

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